PAIN

What causes pain? Is pain subjective? Can pain be quantified? Imaged?

Does pain have “value”?

Do other “life forms” experience pain? (ie: as models)

How good are we in alleviating pain?

Is there a place for “conditioning”?

Can pain be “tolerated”?

Washington
Hospital Center
MedStar Health

GEORGETOWN UNIVERSITY
MEDICAL CENTER

Demystifying Medicine: Pain
How It Happens and What Can Be Done

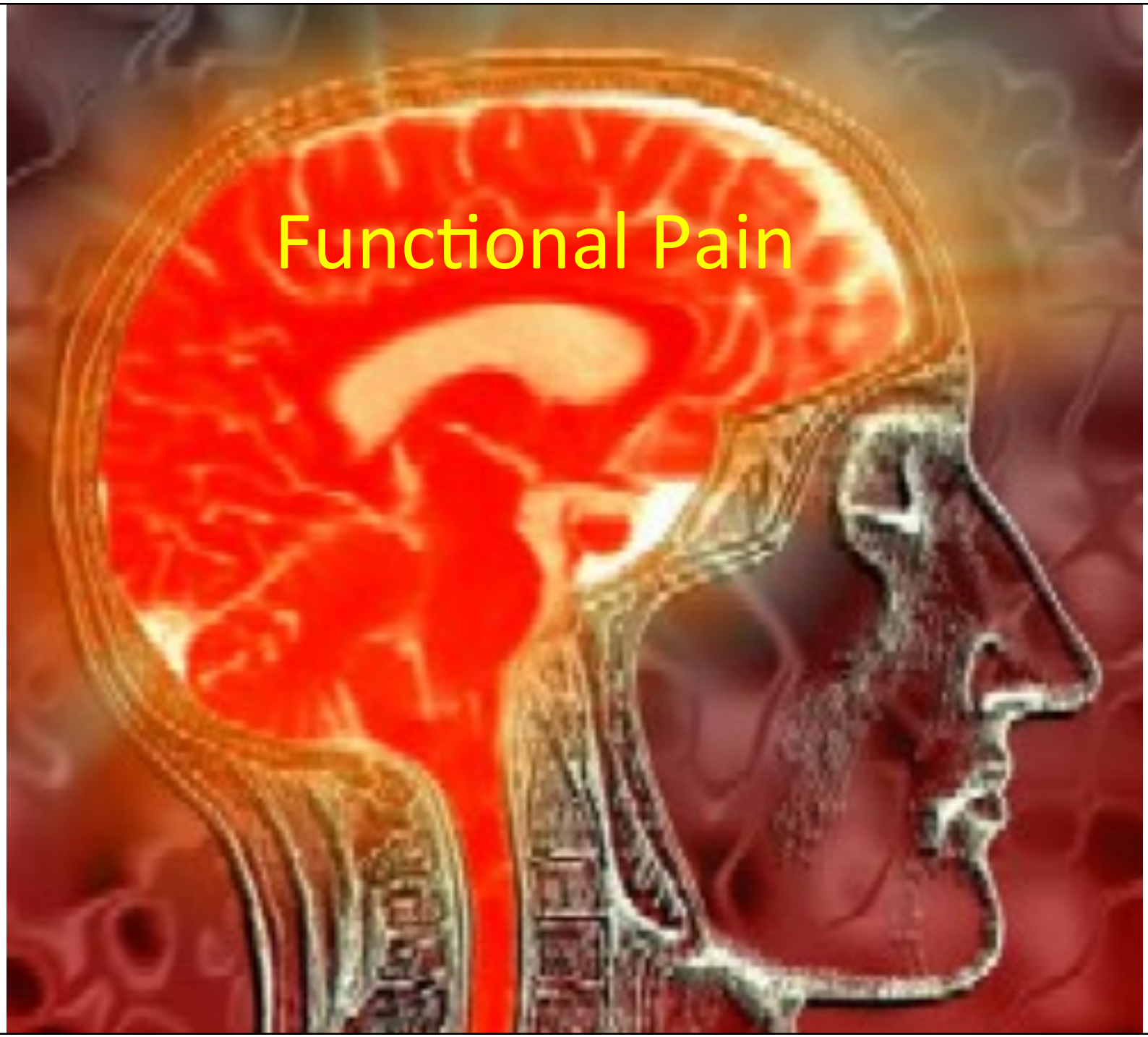
Brian Walitt MD MPH

Special Thanks to our Patient
Melissa

I have no financial conflicts of interests to report

Pain: an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage


Nociceptive
Pain

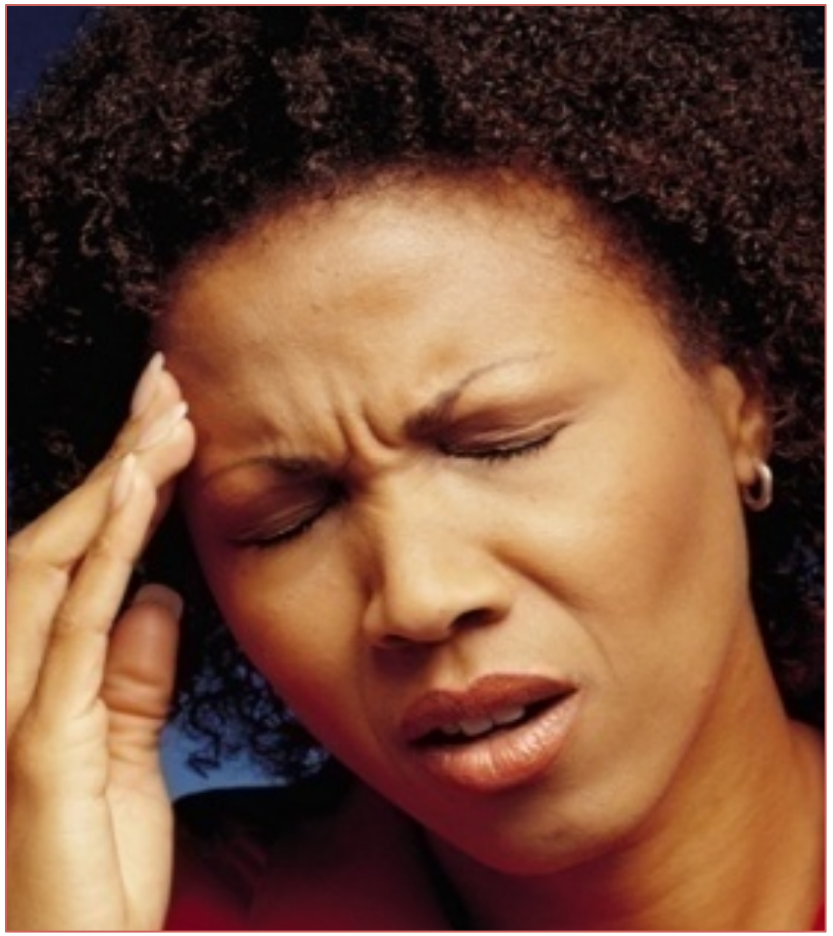

Functional Pain

Low Back Pain

- 15 million medical visits/year
  - 2.5% of all medical visits
- $100 billion/year in medical costs
  - 75% costs due to 5% LBP patients

Tension-Type Headaches

- Affects 38% of the population.
- Chronic symptoms in 2% population



Osteoarthritis

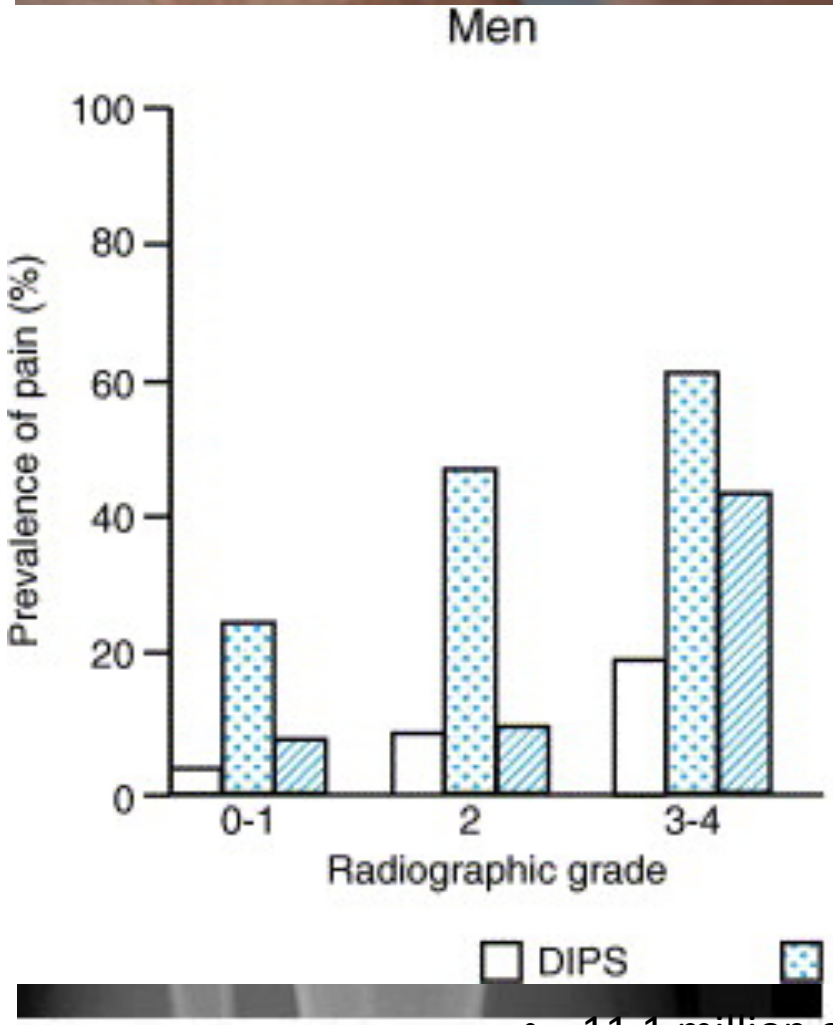


Figure 1

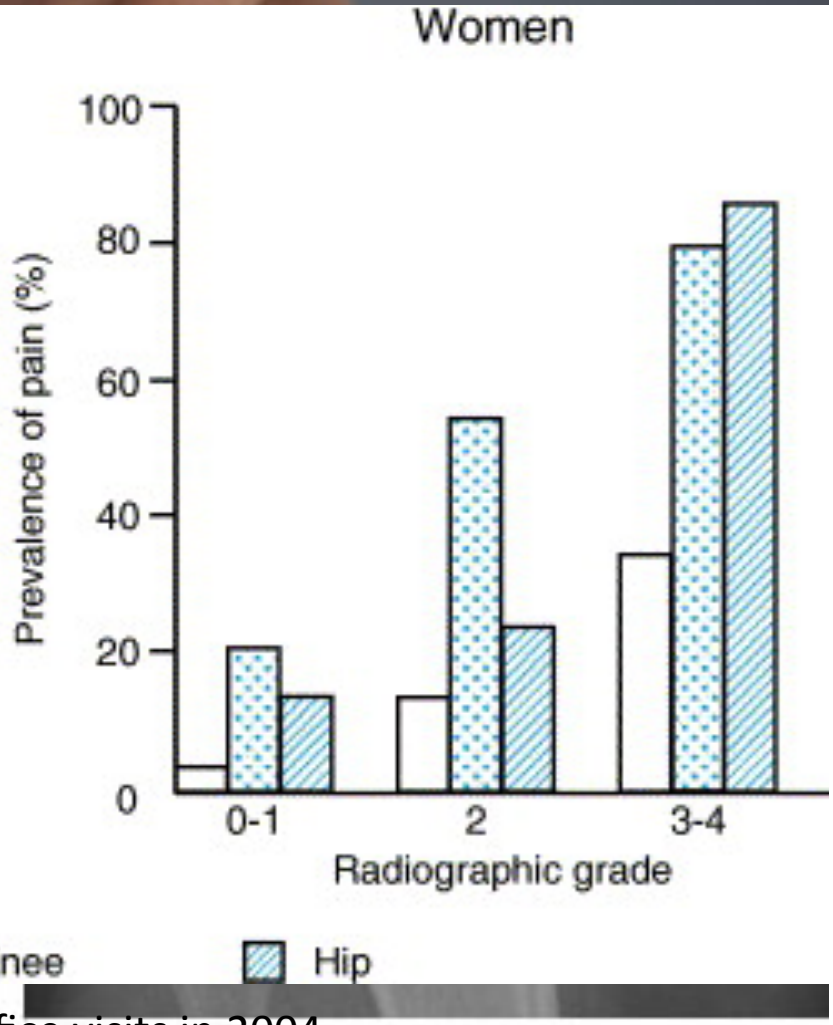
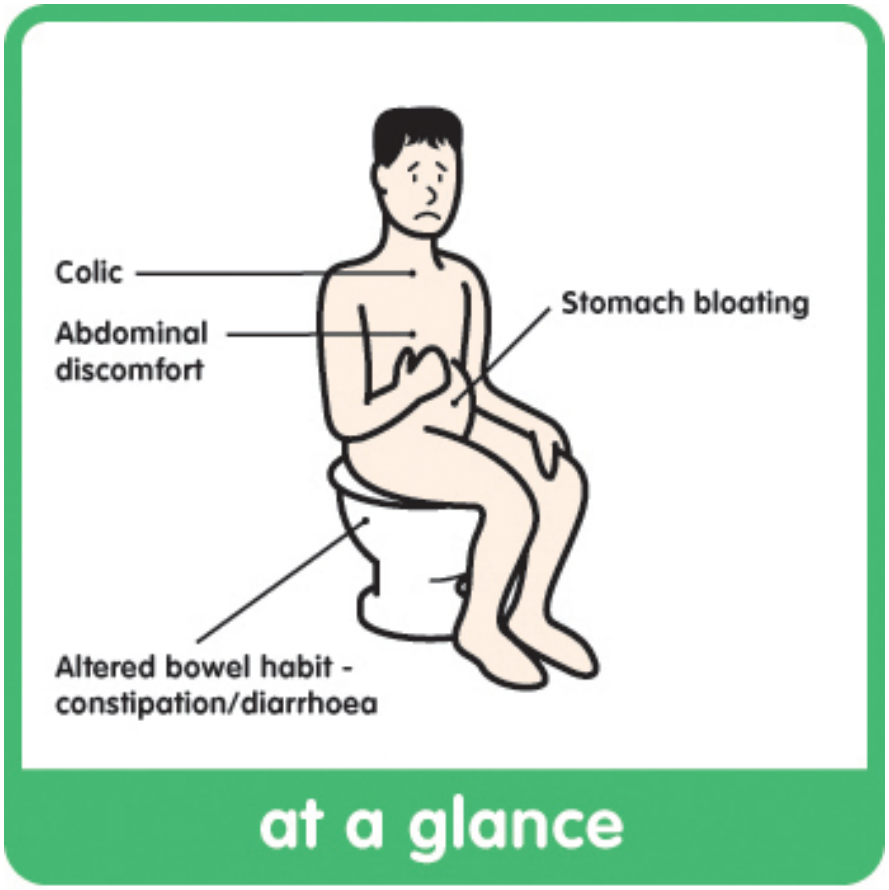


Figure 2

- 11.1 million office visits in 2004
- $186 billion in US medical costs in 2009



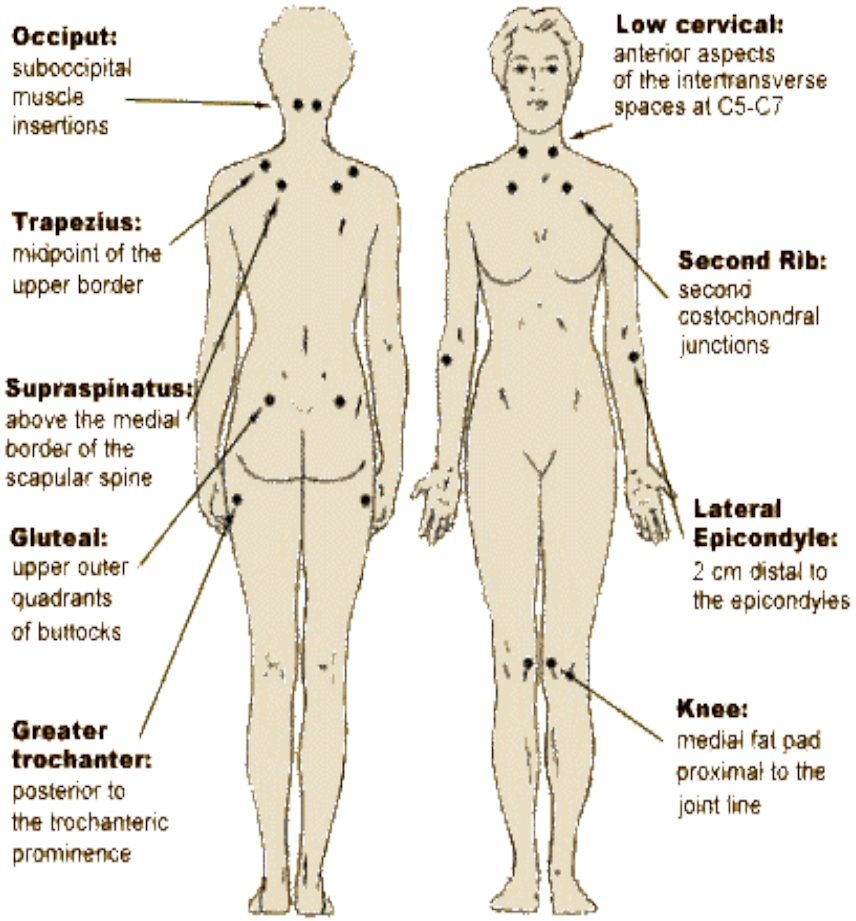
Irritable Bowel Syndrome (IBS)

- 10-15% population have symptoms
- Comprises >25% of all gastroenterologist referrals
- Medical costs estimated at $30 billion/year

Fibromyalgia

- Estimated to affect 4% of the population
- Estimated $12-14 billion/year in US health care costs
- Over 25% of patients with fibromyalgia are disabled

Fibromyalgia



The archetypical functional pain syndrome

- No obvious cause of pain
- Pain > 3 months
- All 4 quadrants of body
- 11/18 Tender points

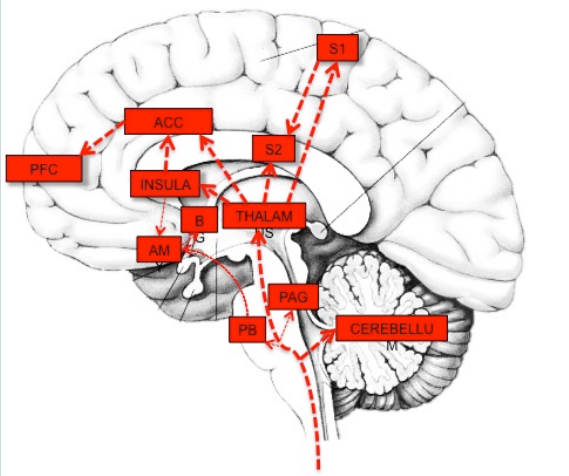
Neck Pain	Interstitial Cystitis
Low Back Pain	Endometriosis
Osteoarthritis	Complex Regional Pain Syndrome
Rheumatoid Arthritis	Phantom Limb Pain
Fibromyalgia	Myofascial Pain Syndrome
Headache	Temporomandibular Disorder
Vulvodynia	Costochondritis
Irritable Bowel Syndrome	Burning Mouth Syndrome

- Discordance between objective injury and subjective pain experience define all of functional pain disorders
- Do these different functional pain disorders share a common biology in the brain?
- What factors can create meaningful changes in their common biology?
- Can we successfully treat functional pain disorders by medically altering this common biology?

There are 3 levels of pain:
Pain, excruciating pain, and
stepping on a Lego.

The neurobiology of pain

M. CATHERINE BUSHNELL
NCCAM/NIH



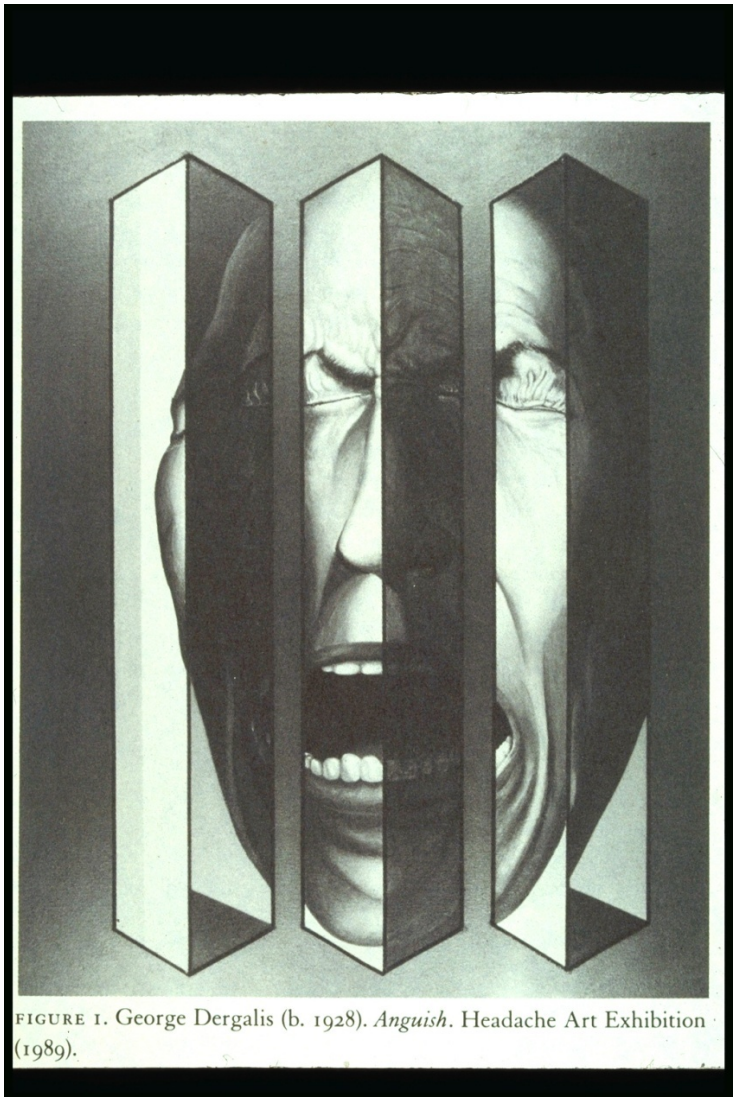
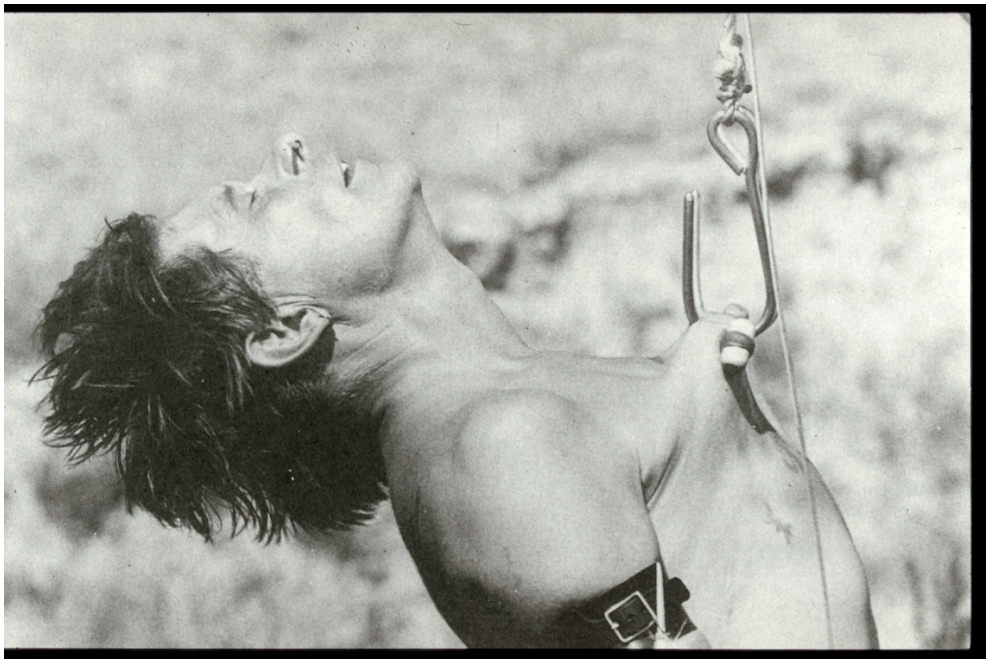
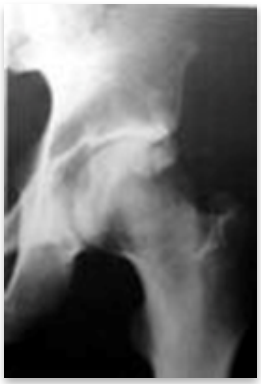
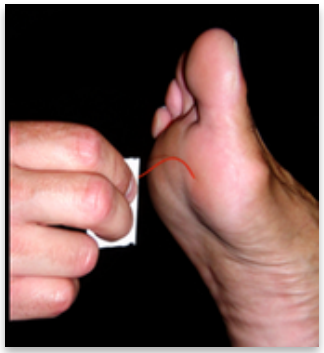
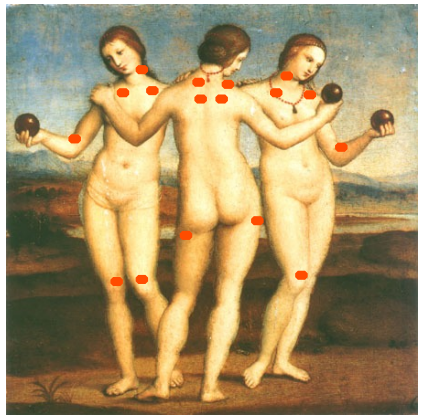


FIGURE 1. George Dergalis (b. 1928). *Anguish*. Headache Art Exhibition (1989).

Pain is a complex sensory and affective experience



There Are Multiple Distinct Pains Each with Different Causes and Underlying Mechanisms

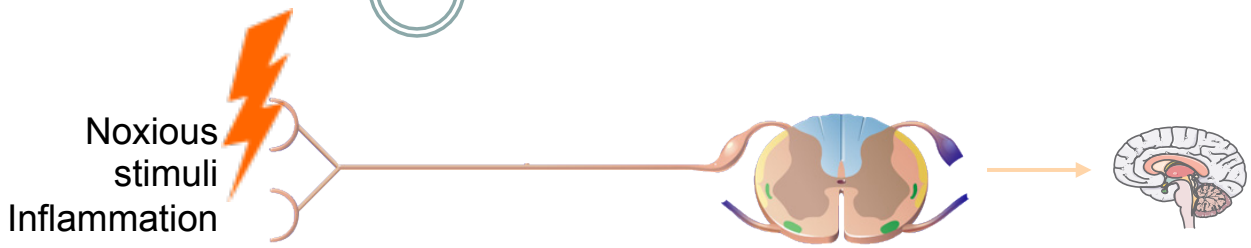
Nociceptive Pain	Nociceptive Pain	Neuropathic Pain	Functional Pain
			
Noxious stimulus Pinch/pinprick Intense heat/cold Acute trauma	Post-operative pain Post-trauma Arthritis Inflammatory	PNS and CNS lesions PHN/PDN/SCI	Fibromyalgia
Protective	Healing/repair or pathological	Pathological	Pathological

CNS=Central nervous system; IBS=Irritable bowel syndrome; PDN=Painful diabetic neuropathy; PHN=Post-herpetic neuralgia; PNS=Peripheral nervous system; SCI=Spinal cord injury.

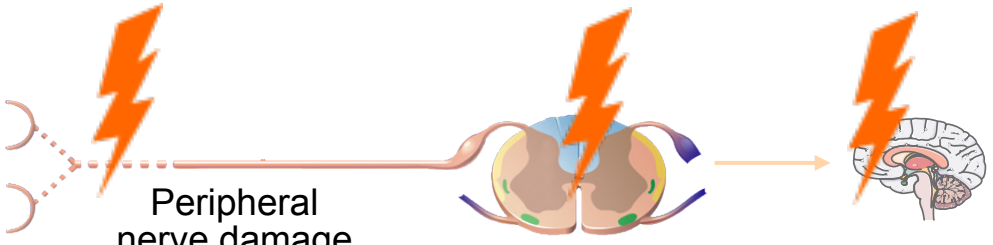
1. Woolf et al. *Ann Intern Med* 2004;140(6):441-51.

Multiple Types of Pain

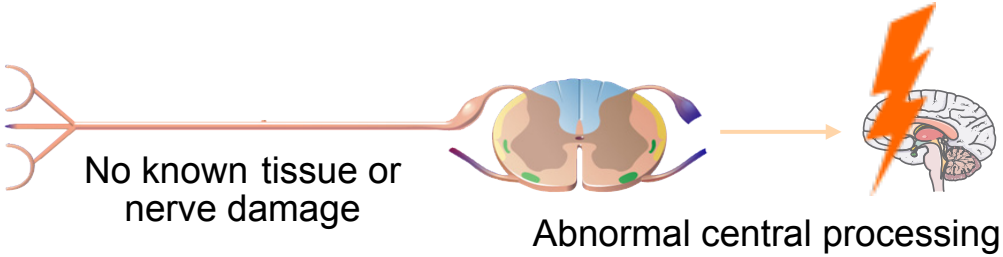
Nociceptive pain



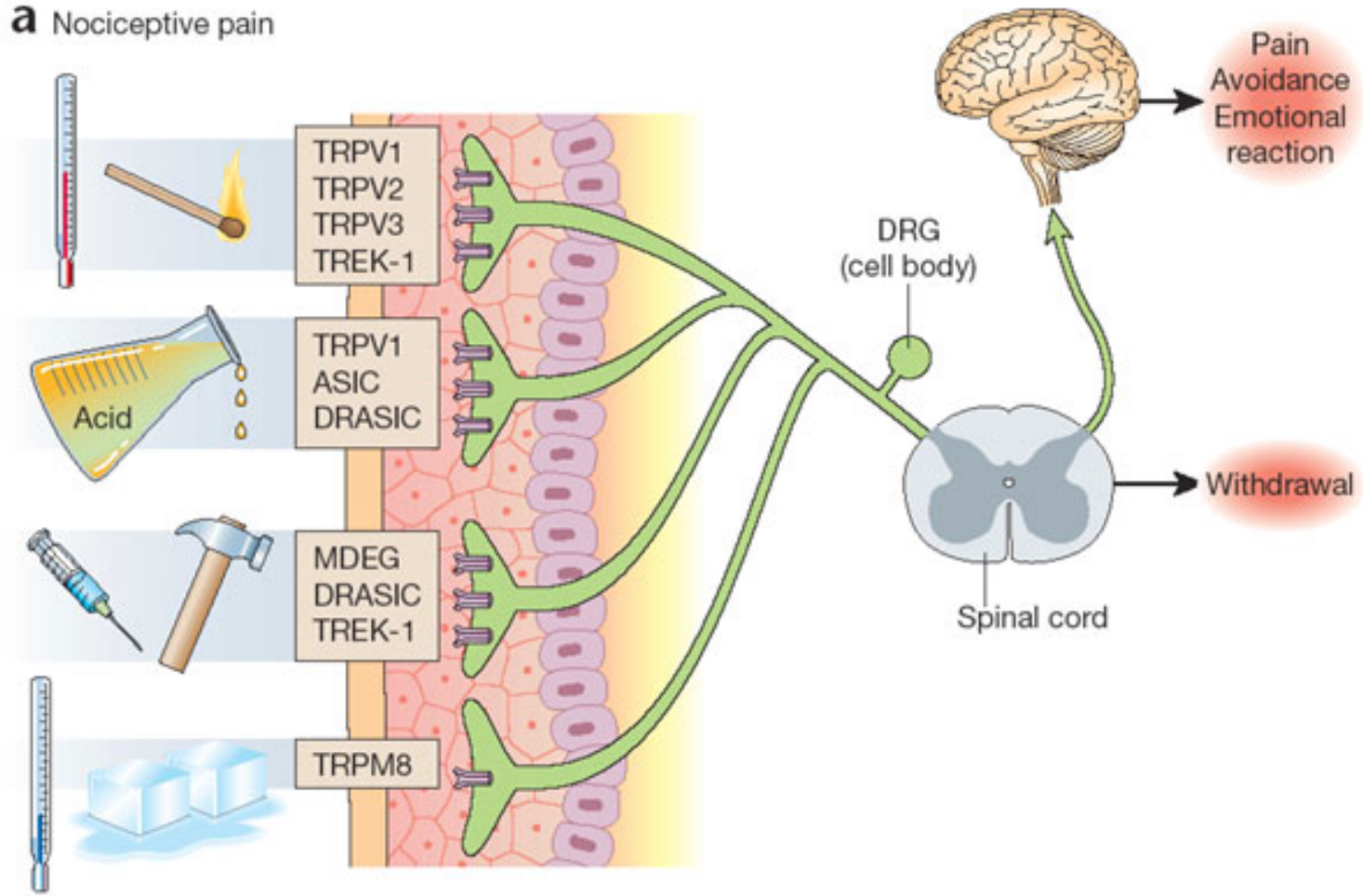
Neuropathic pain



Functional pain
(non-inflammatory
non-neuropathic)

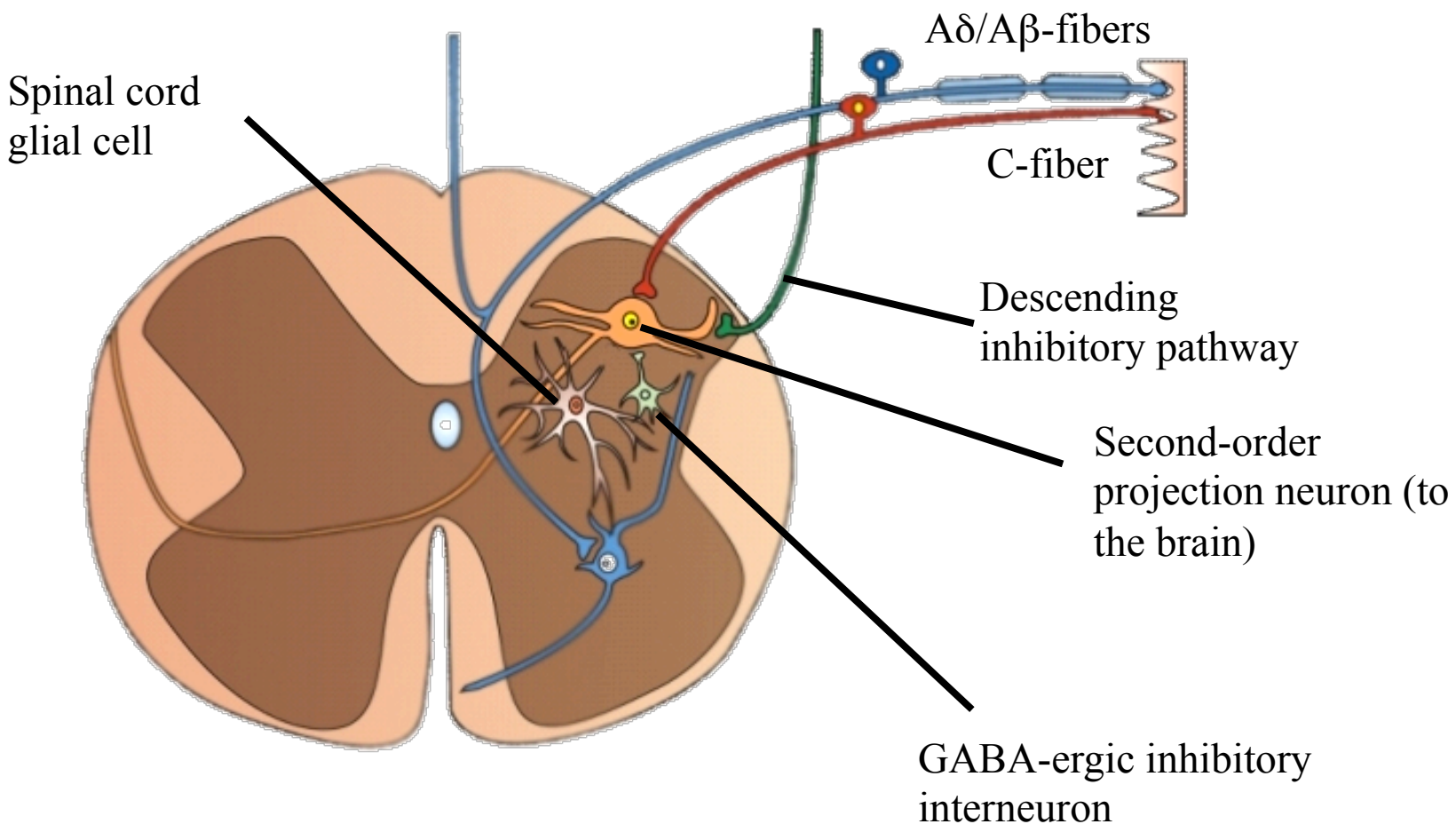


Figures adapted from: Woolf. *Ann Intern Med* 2004;140(6):441-51.



Transduction mechanisms of nociceptive pain

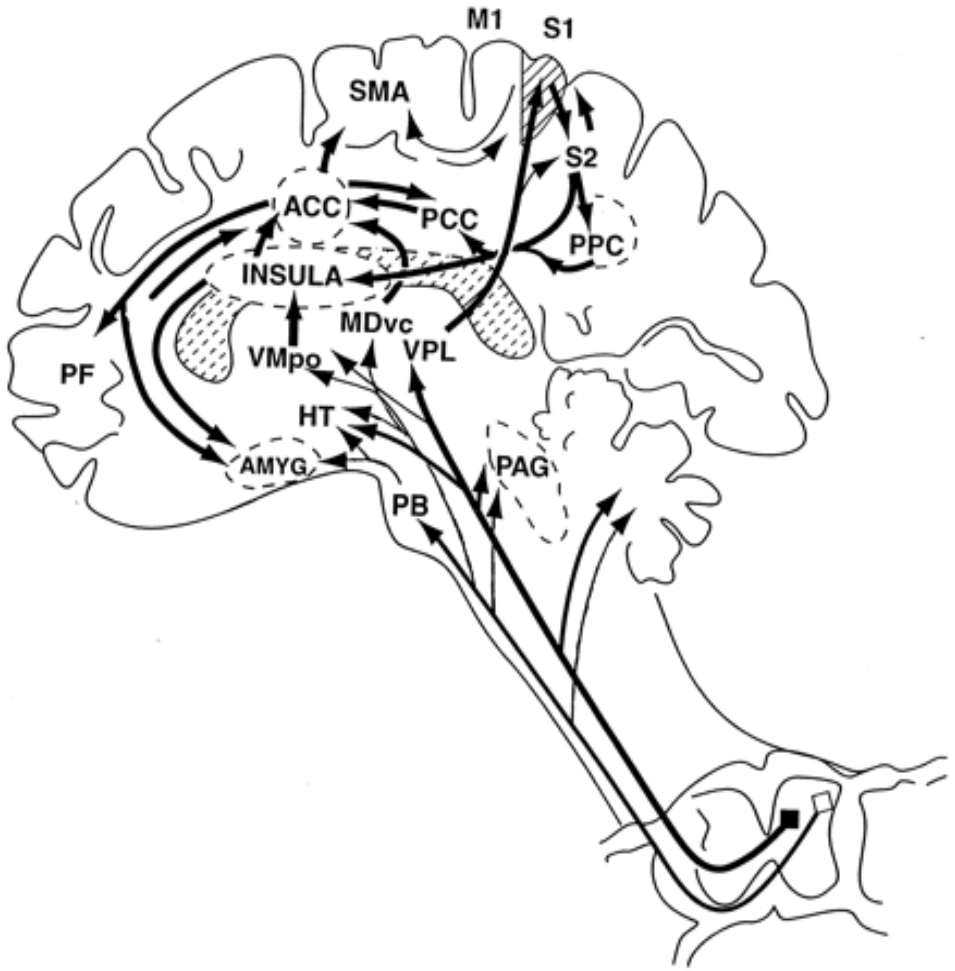
Spinal cord dorsal horn



GABA= γ -aminobutyric acid.

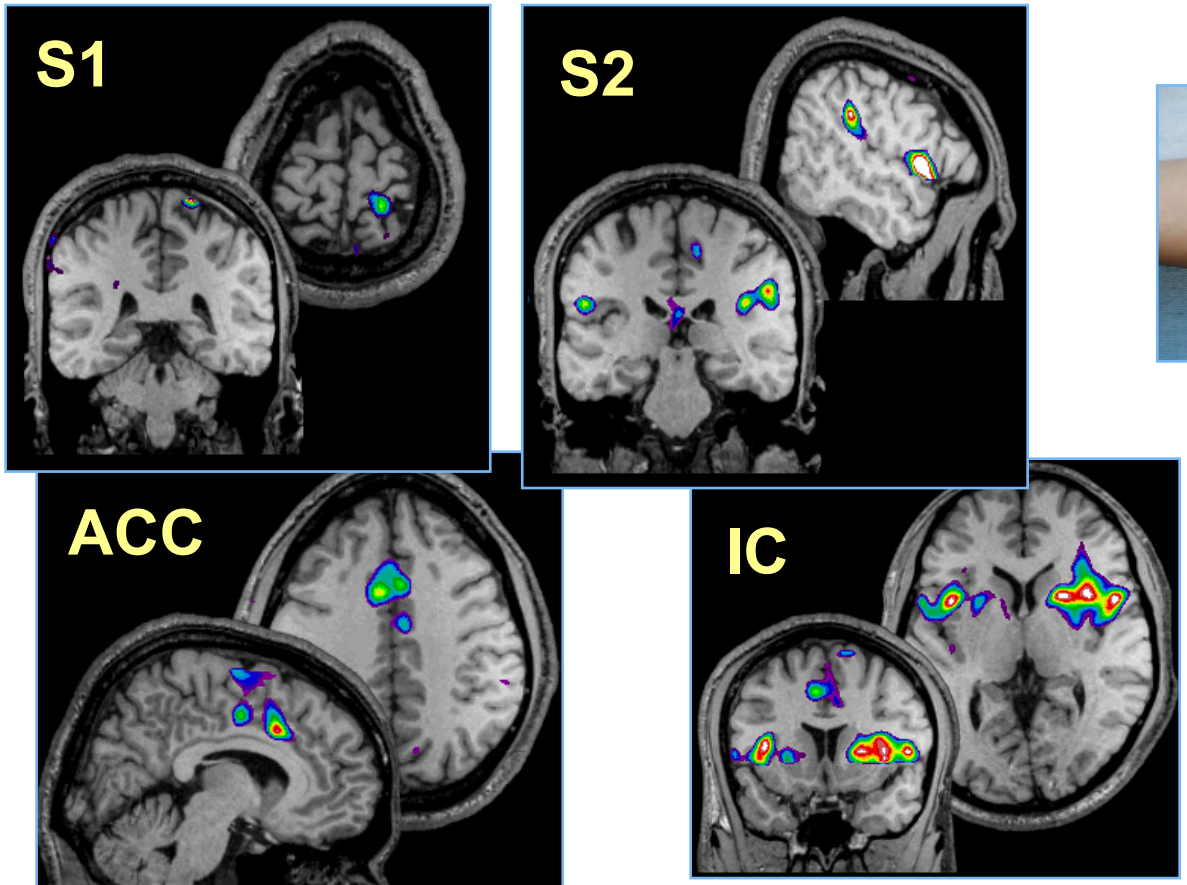
Baron. *Nat Clin Pract Neurol* 2006;2(2):95-106.

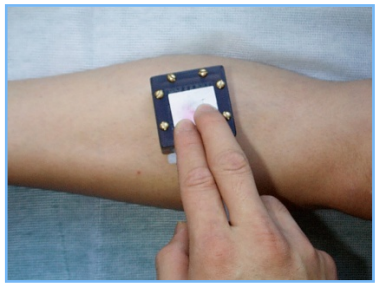
Forebrain pain mechanisms



D.D. Price, Science 2000

Sensory and affective brain regions activated by pain

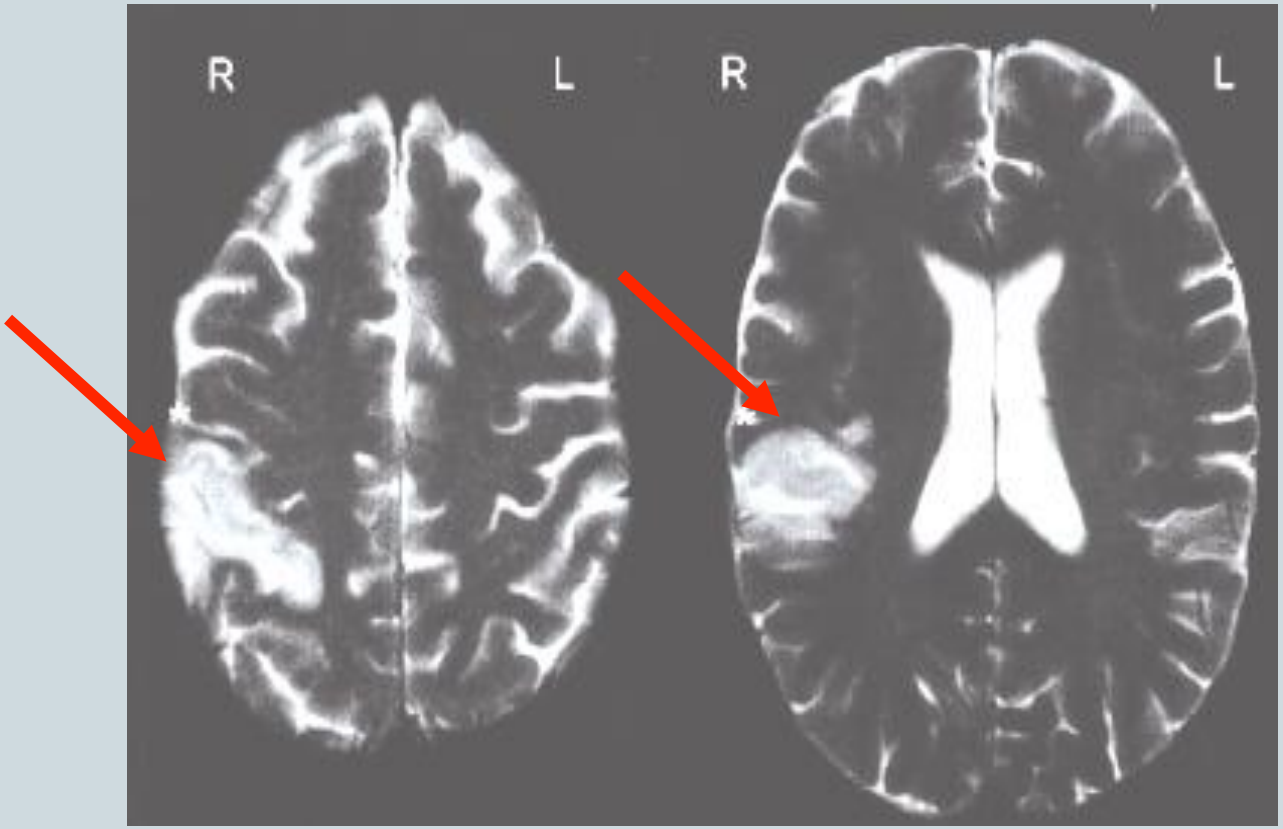




ACC: Anterior cingulate cortex; IC: Insular cortex.

Apkarian A, et al. *Eur J Pain*. 2005;9:463–485.

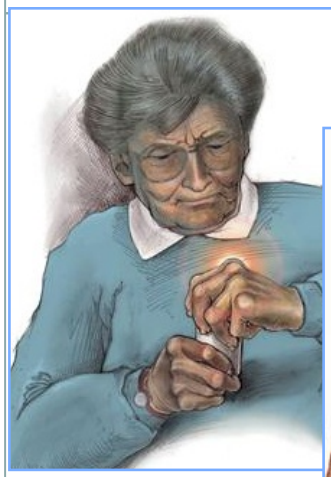
Sensory and limbic regions have different roles in pain processing

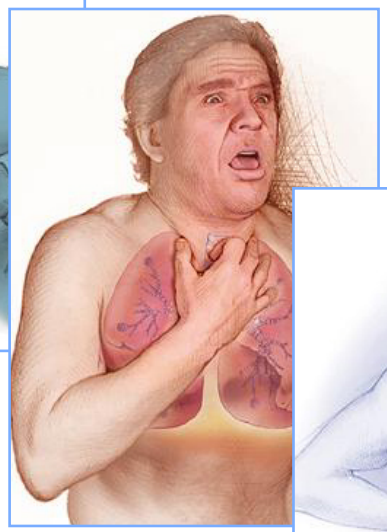


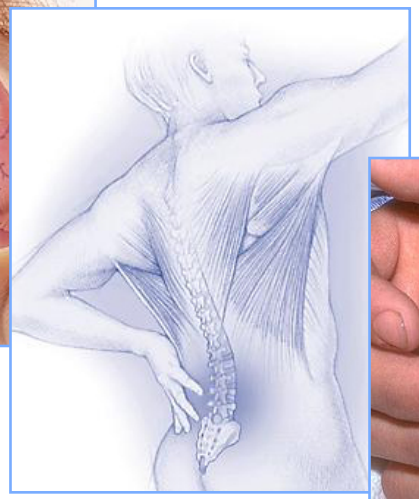
Pain affect without "pain sensation" in patient with postcentral lesion

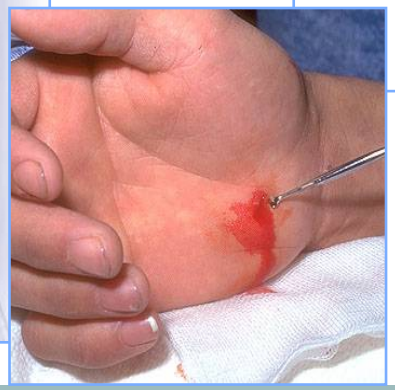
Ploner et al. 1999

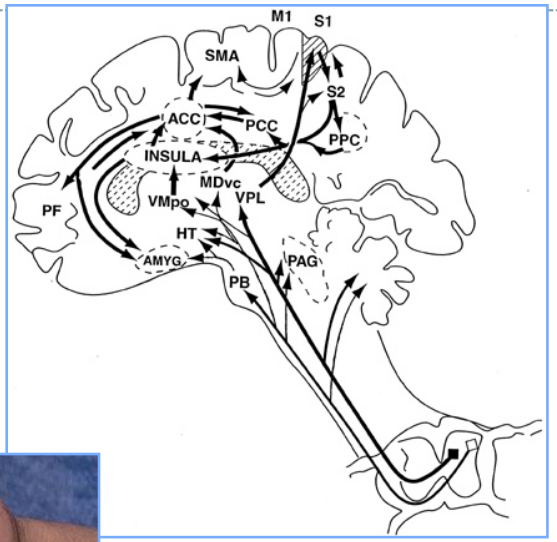
Pain network activated by many types of pain



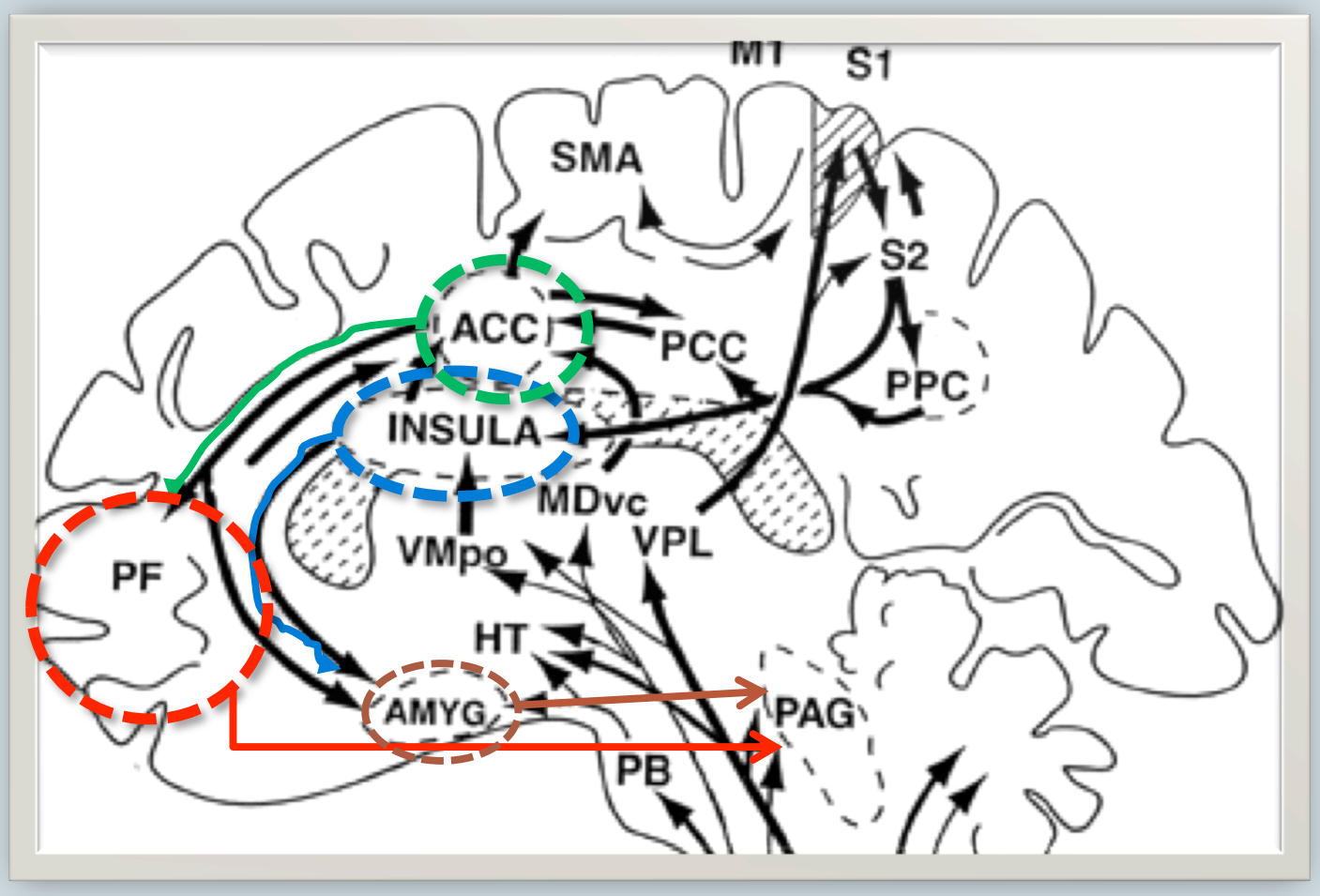






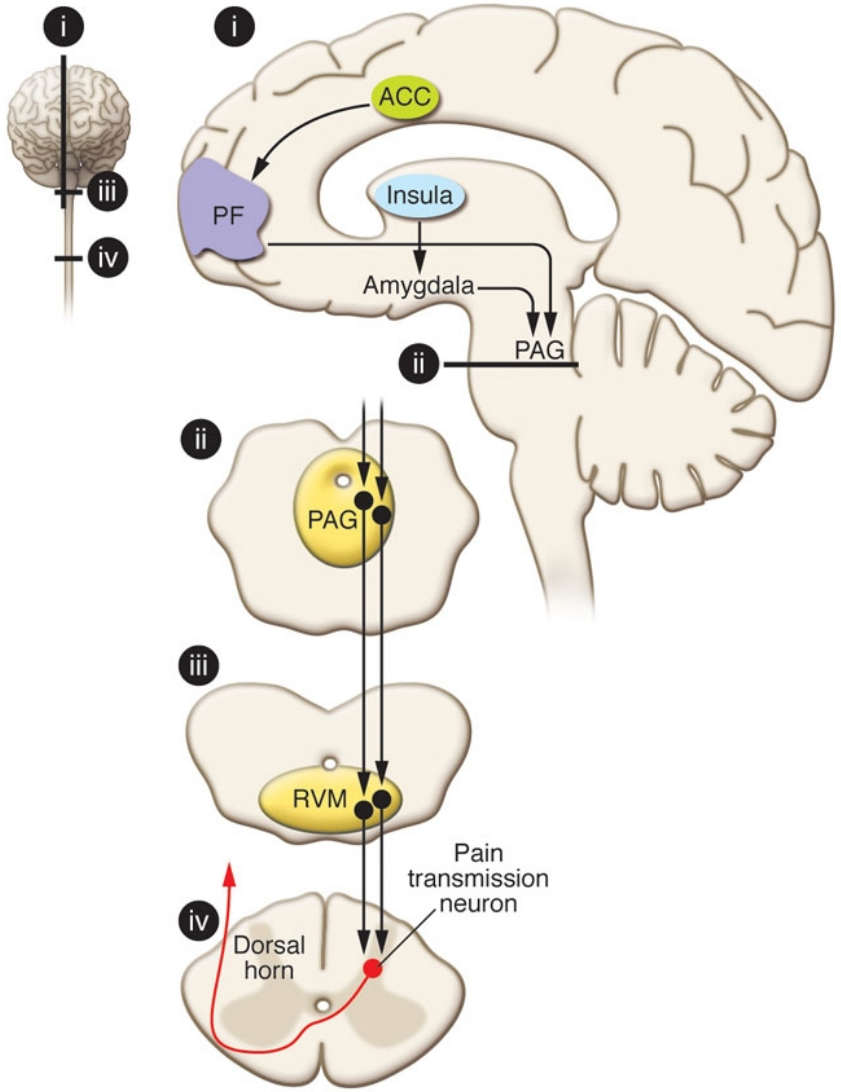


Some cortical regions are involved in descending pain modulation



Descending modulation of pain

Information from cortex ultimately received in spinal cord



Schweinhardt and Bushnell, J. Clin. Investigation, 2010.

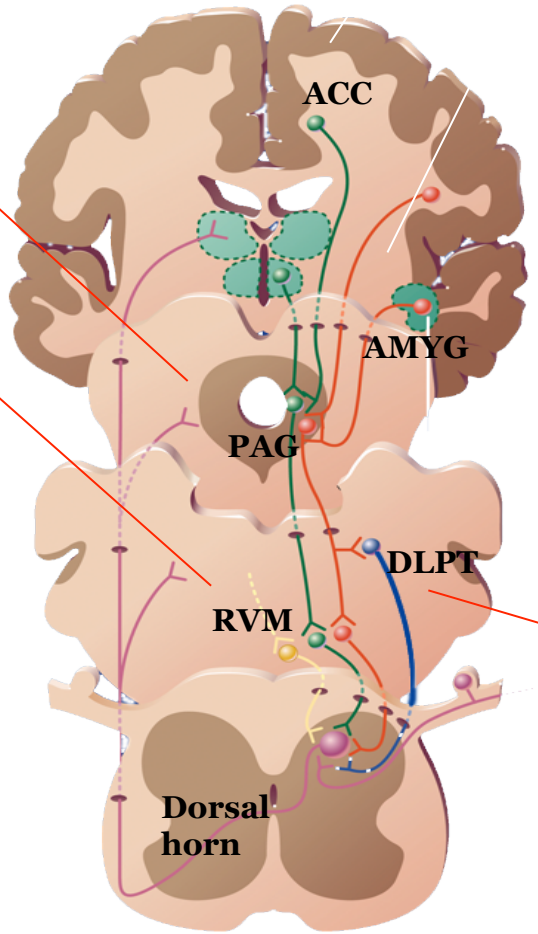
Descending pathways can facilitate or inhibit pain[1–3]

PAG

RVM

Facilitatory

Aspartate
Glutamate
Serotonin



Inhibitory

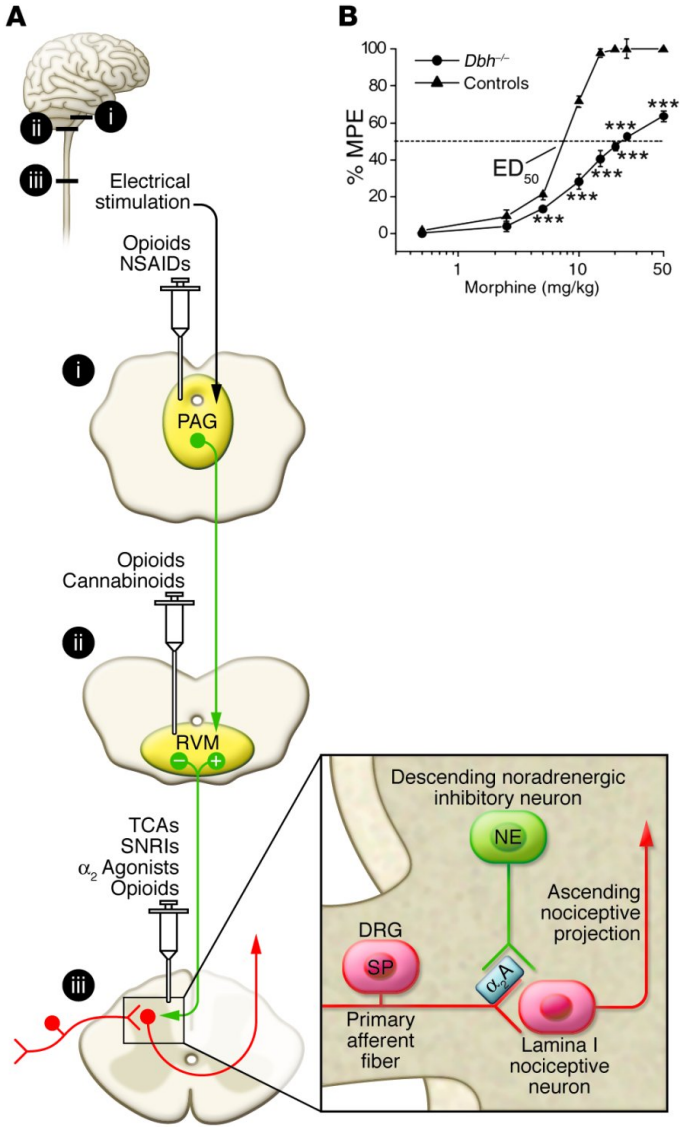
Dopamine
Glutamate
γ-aminobutyric acid (GABA)
Noradrenaline
Opioids
Serotonin

PAG
Dorsolateral pontine tegmentum (DLPT)
RVM

1. Fields HL, et al. 1991. 2. Vanegas H, Schaible H-G. 2004.
3. Ren K, Dubner R. 2007.

Descending pathways are central targets for analgesic drugs.

But how are they activated naturally?



Ossipov et al, J. Clin. Investigation, 2010.

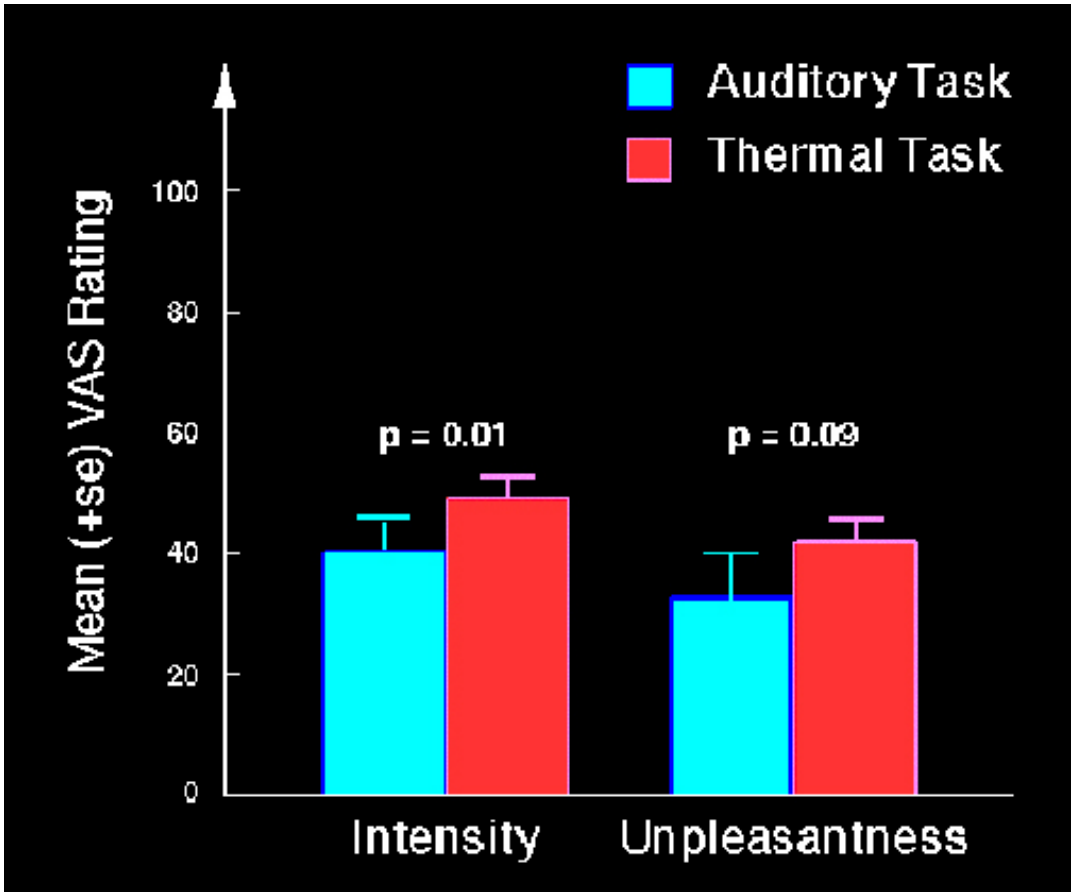
Psychological factors modulate pain via these descending modulatory pathways

Emotions

Attention

How do psychological conditions alter pain?

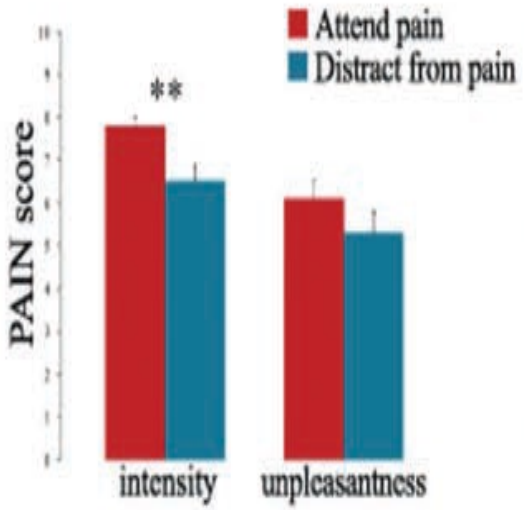
Attention Modulates Pain



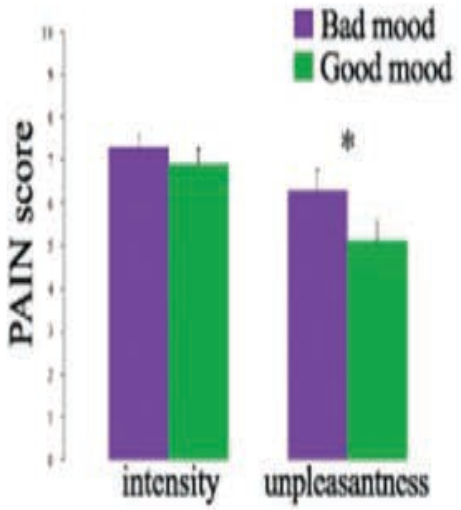
Bushnell et al. 1999

Emotions alter pain differently than attention

ATTENTIONAL MODULATION

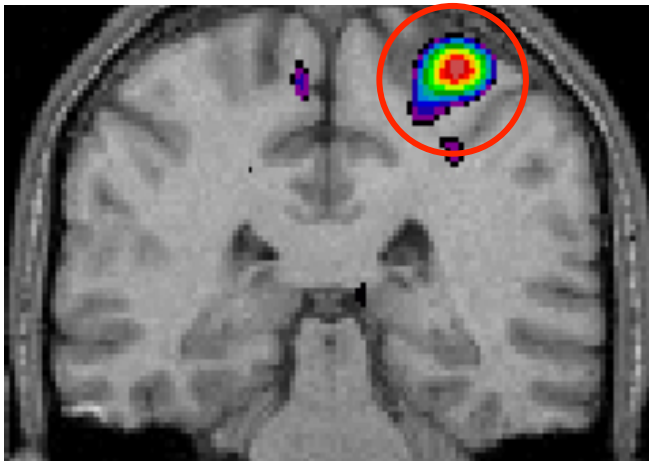


EMOTIONAL MODULATION

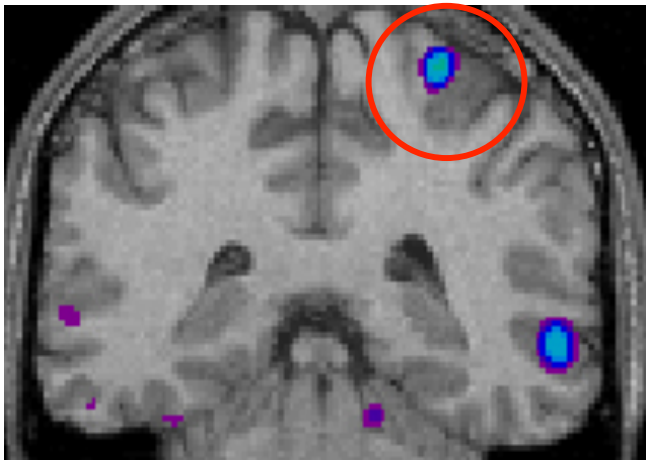


Villemure et al 2003; Villemure & Bushnell 2009

Attention Modulates Pain



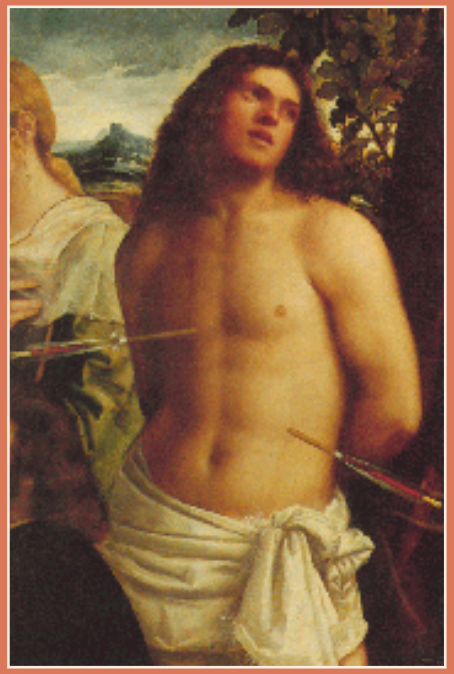
Attention to pain



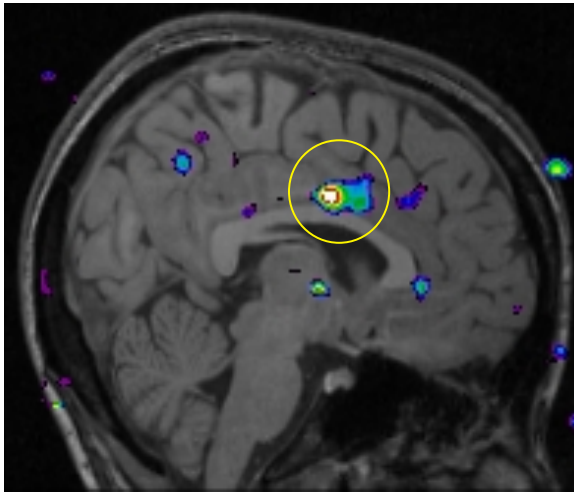
Distraction from pain

Bushnell et al. 1999

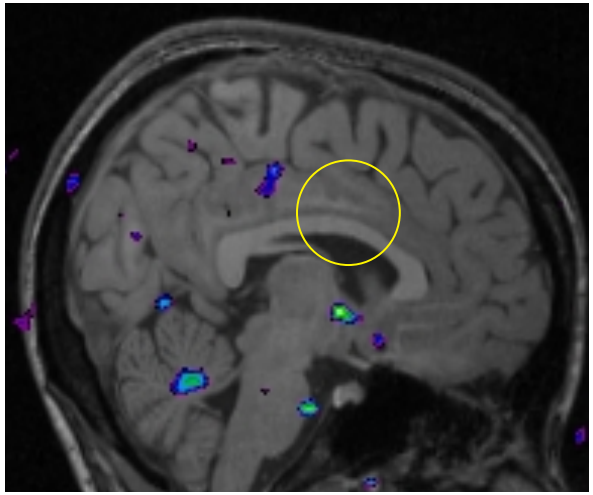
Emotions alters pain



Mood alters pain-evoked activity in limbic brain regions



Bad mood + Pain

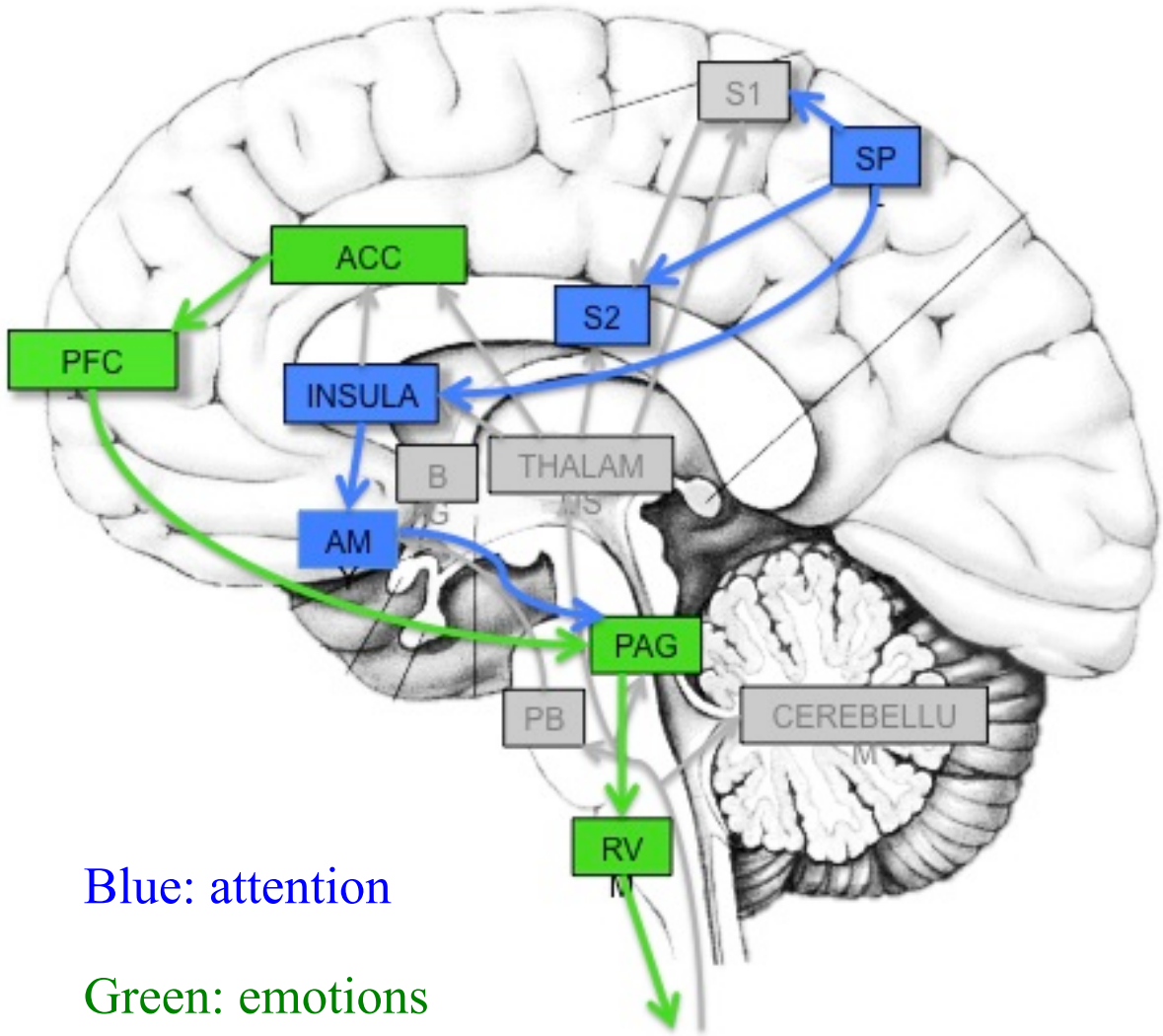


Good mood + Pain

Anterior cingulate cortex

Villemure & Bushnell 2009

Attention and emotion activate different modulatory circuitry in brain



Blue: attention

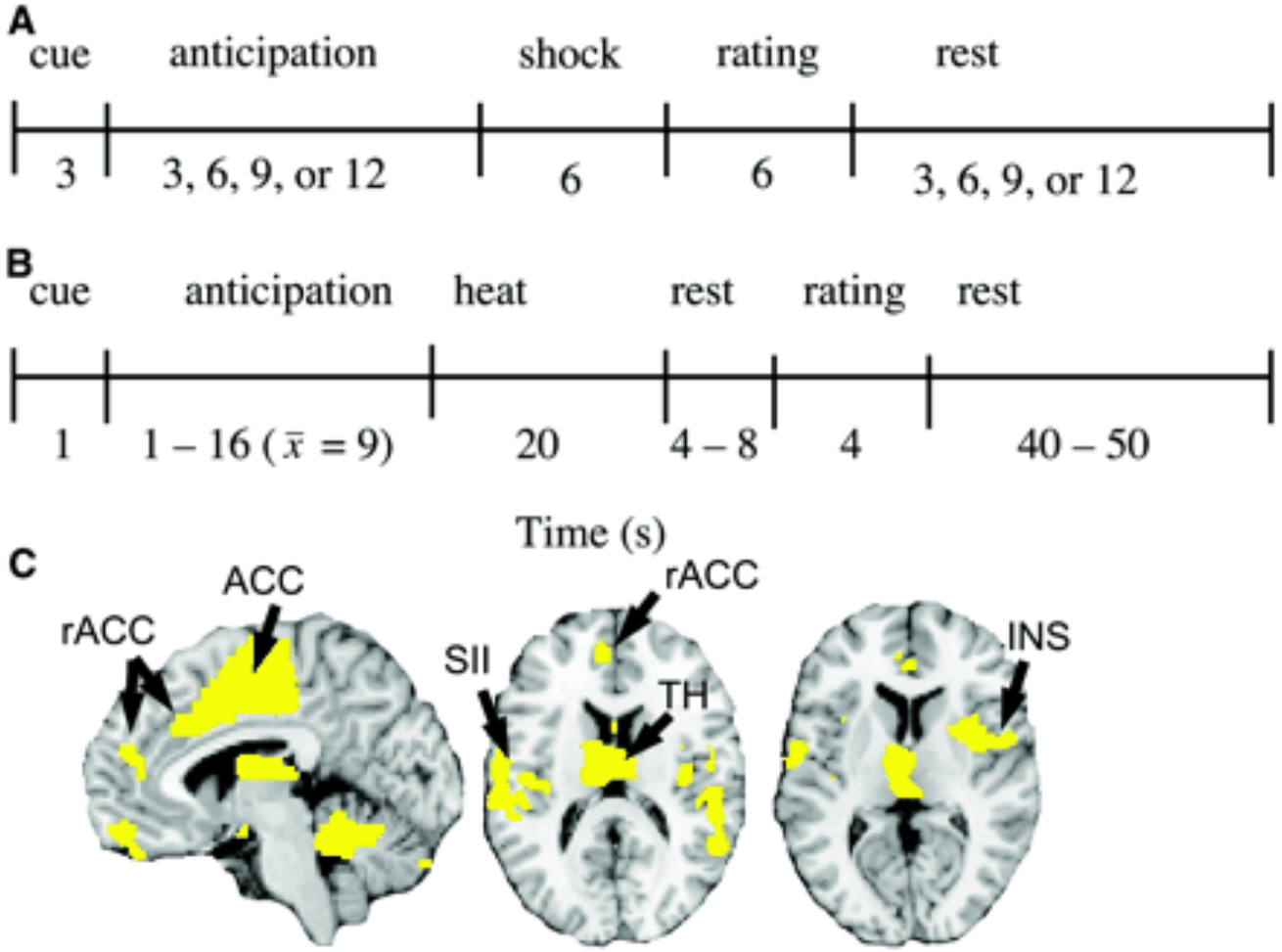
Green: emotions

Villemure C, et al. *J Neurosci*. 2009.

Bushnell, Ceko, Low, in press

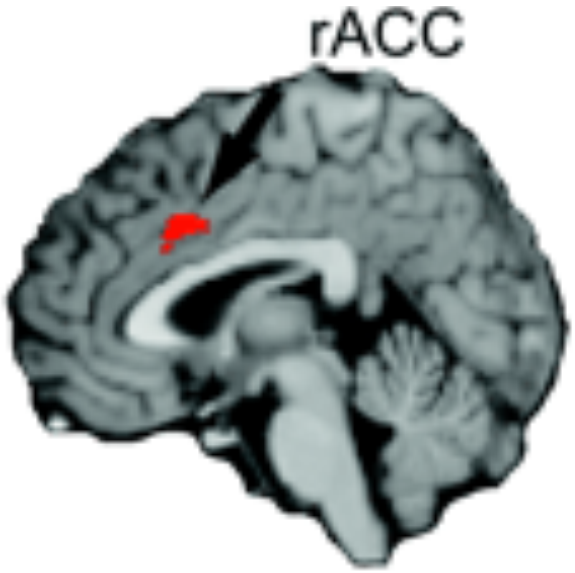
Placebo Analgesia

Imaging placebo analgesia

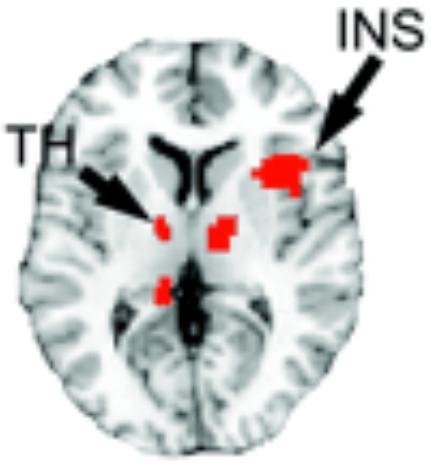


Wager et al 2004 *Science*

Imaging placebo analgesia

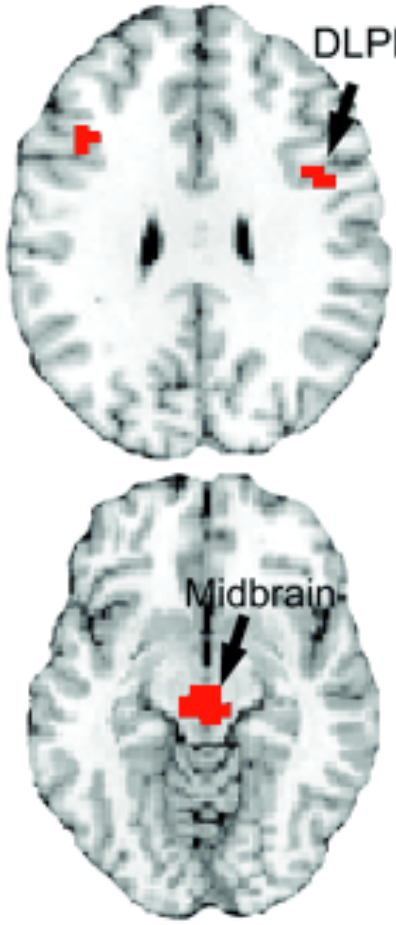


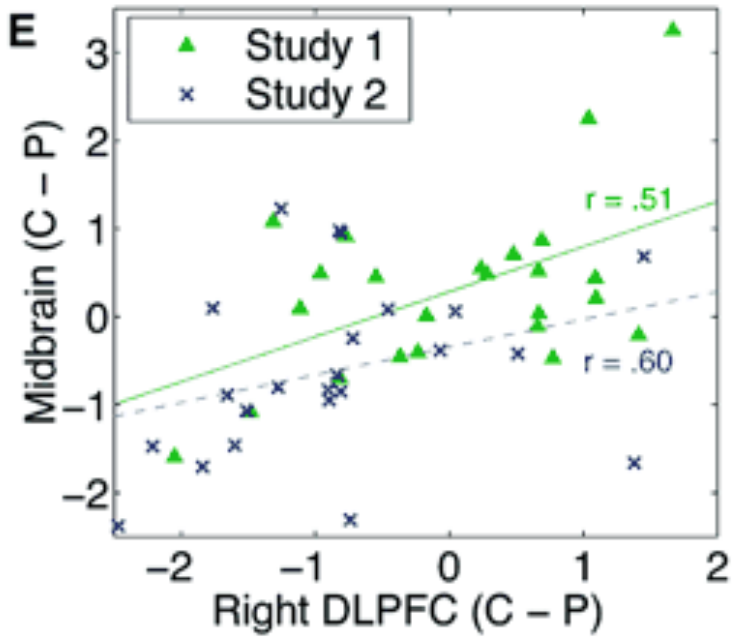
Placebo reduces pain-evoked activity in ACC, insula and thalamus



Wager et al 2004 *Science*

Imaging placebo analgesia

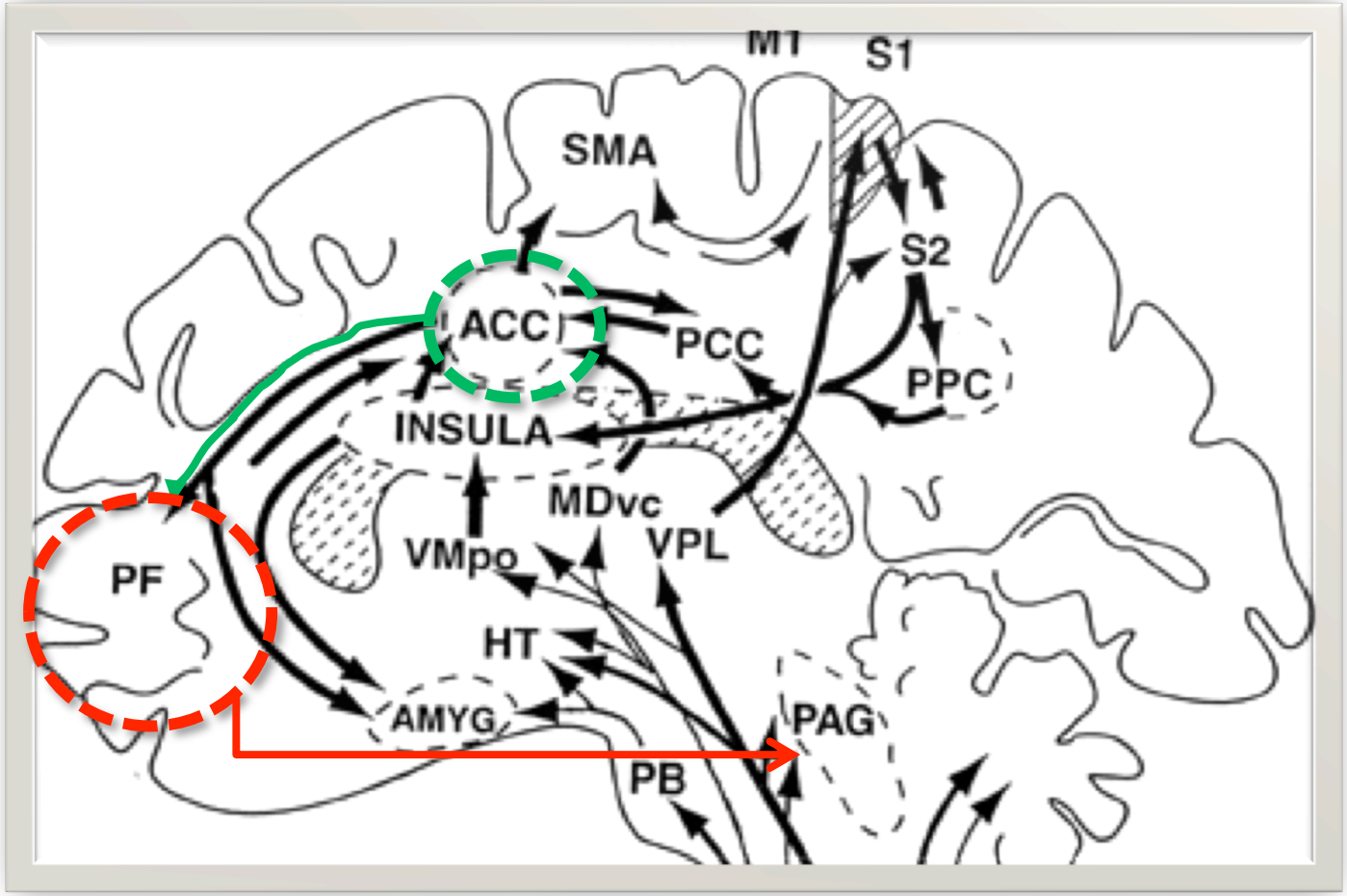




Placebo increased prefrontal and midbrain activity in anticipation of pain

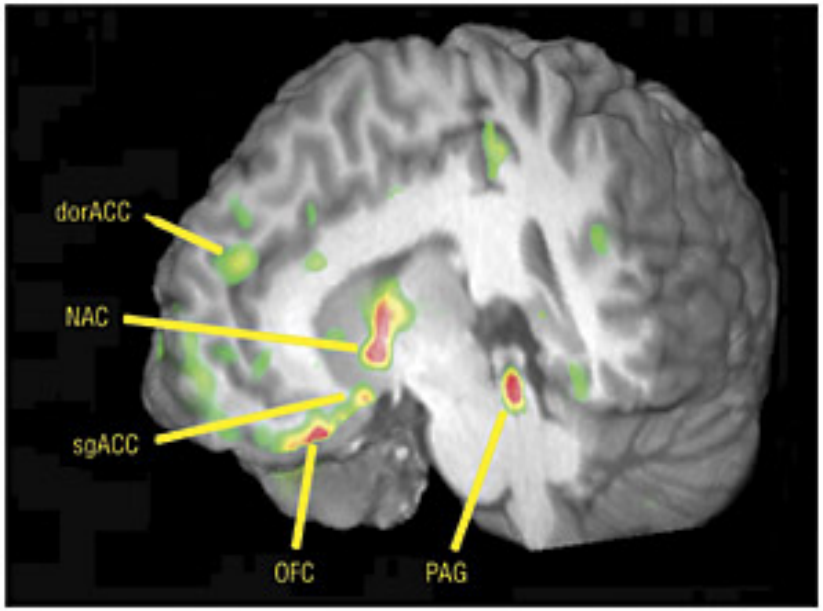
Wager et al 2004 *Science*

Placebo activates similar descending system as does emotional modulation



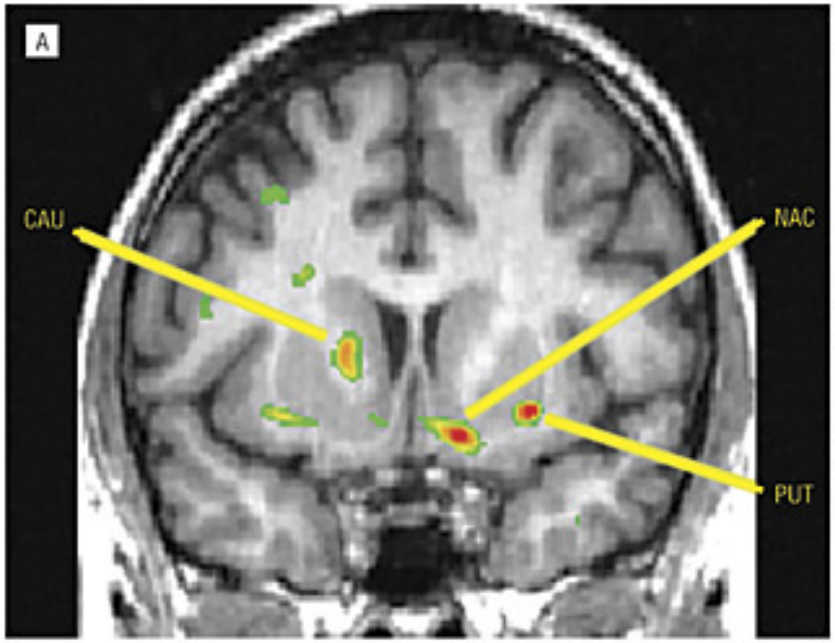
Price DD. *Science*. 2000;288:1769-1771.

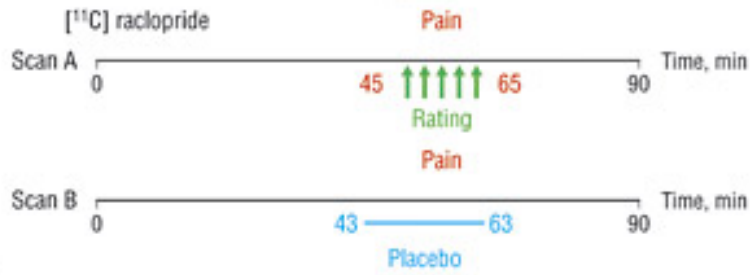
Placebo activates mu-opioid receptors



Scott, D. J. et al. Arch Gen Psychiatry 2008;65:220-231.

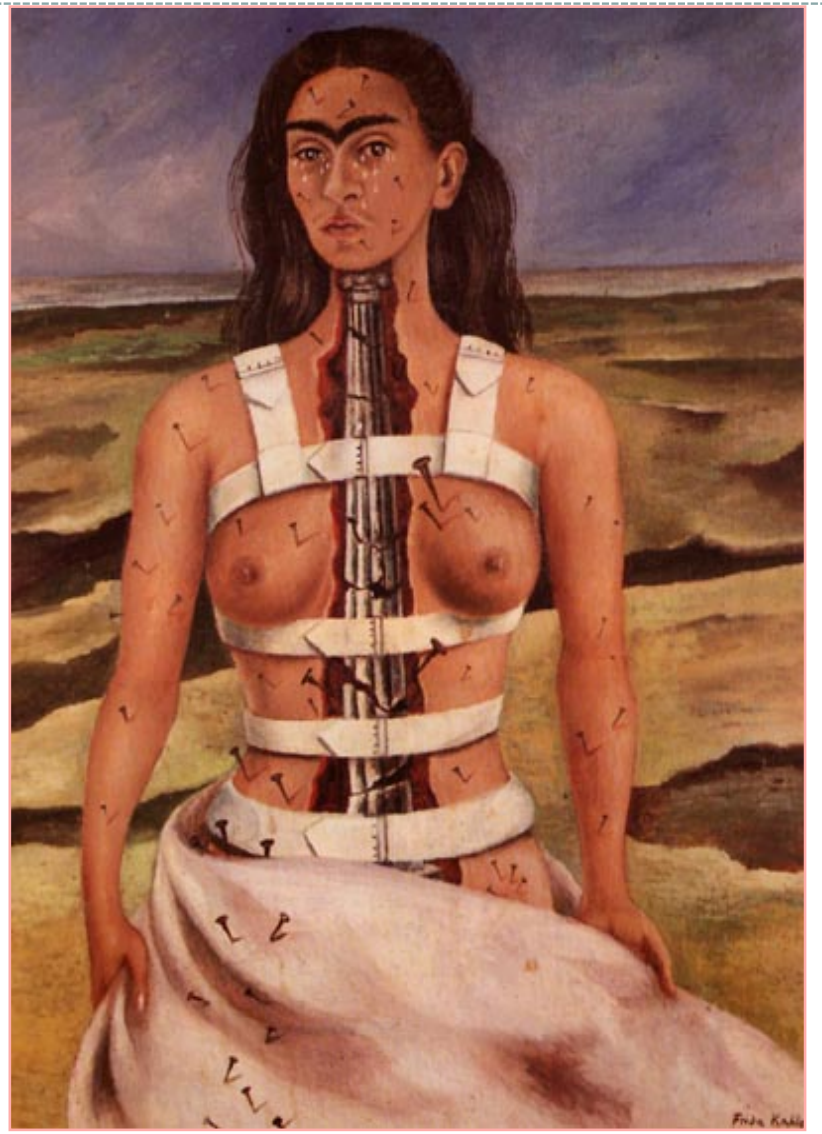
Placebo activates dopamine D2/D3 receptors





Scott, D. J. et al. Arch Gen Psychiatry 2008;65:220-231.

Central neuroplasticity with chronic pain



Frida Kahlo

Central sensitization

"INCREASE IN THE EXCITABILITY OF THE CENTRAL NERVOUS SYSTEM SO THAT NORMAL INPUTS NOW EVOKE EXAGGERATED RESPONSES"

Woolf CJ. *Nature*. 1983;306:686–688.

Neuroplasticity in Spinal Cord Processing: Central Sensitization

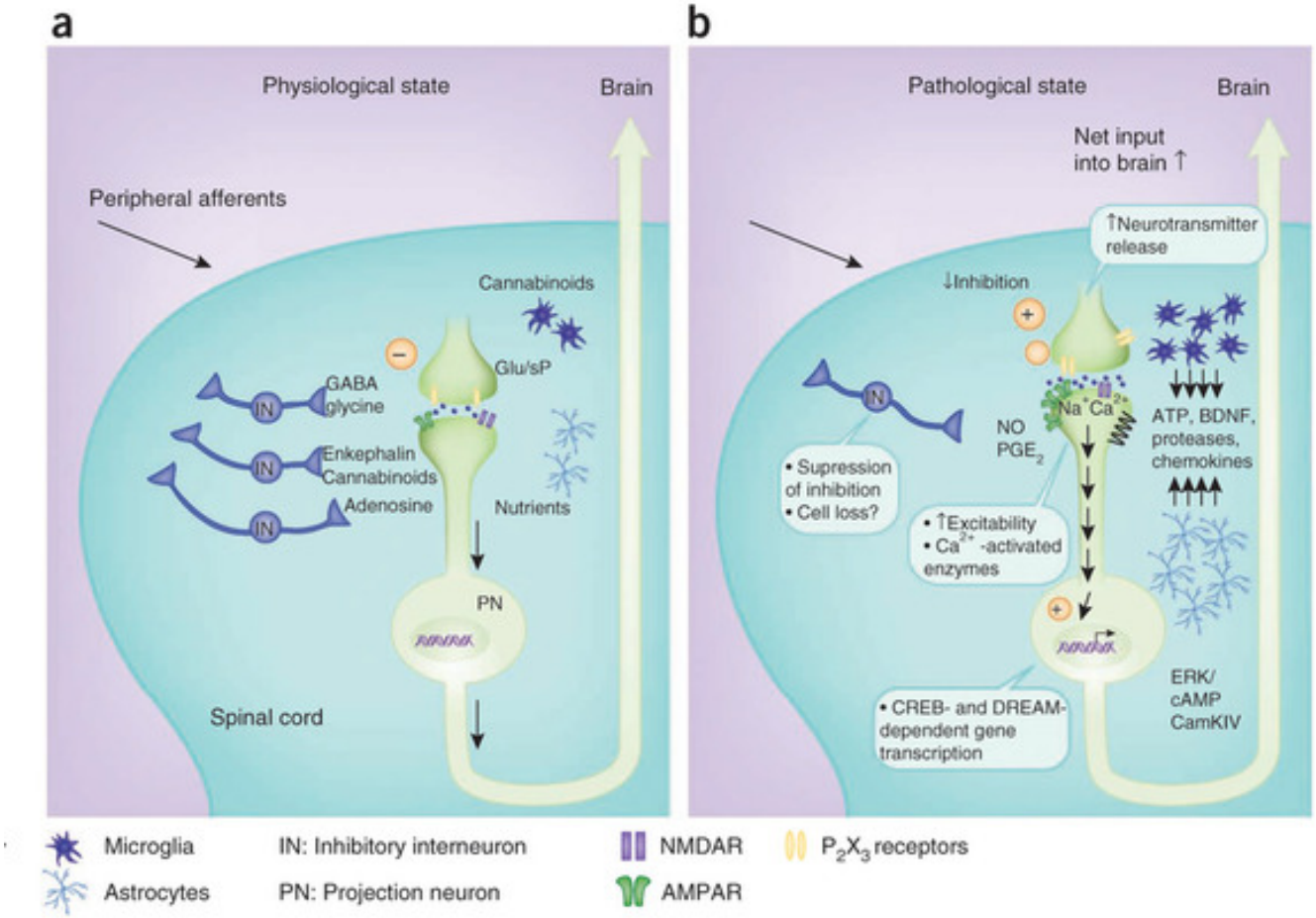
- Potential mechanisms:
  - NMDA receptor activation[1,2]
  - Decreased inhibition[2]
  - Microglial activation[3]
  - Altered gene expression in dorsal horn neurons[4]
  - Synaptic plasticity, reorganization[4]

- Further leading to thalamic and cortical changes[4,5]

NMDA=*N*-methyl-D-aspartic acid.

1. Mannion et al. *Clin J Pain* 2000;16(Suppl 3):S144-56. 2. Ossipov et al. *Ann NY Acad Sci* 2000;909:12-24.
3. Wieseler-Frank et al. *Neurosignals* 2005;14(4):166-74. 4. Navarro et al. *Prog Neurobiol* 2007;82(4):163-201.
5. Guilbaud et al. *Exp Brain Res* 1992;92(2):227-45.

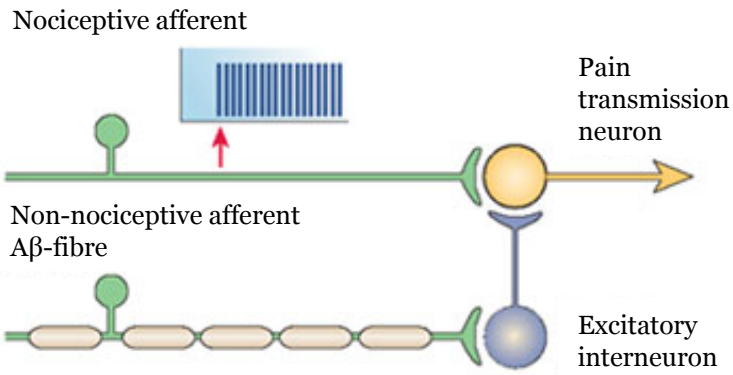
Synaptic plasticity in spinal cord dorsal horn



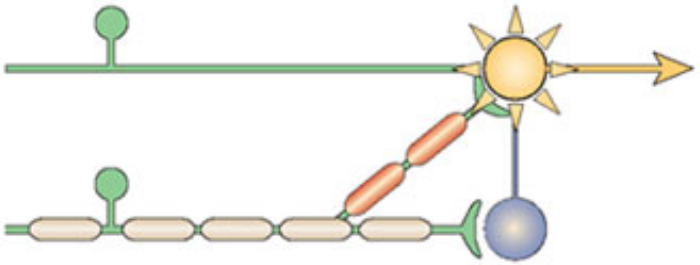
Kunar, Nat. Med. 2010

Changes in synaptic connectivity and loss of inhibition in spinal cord

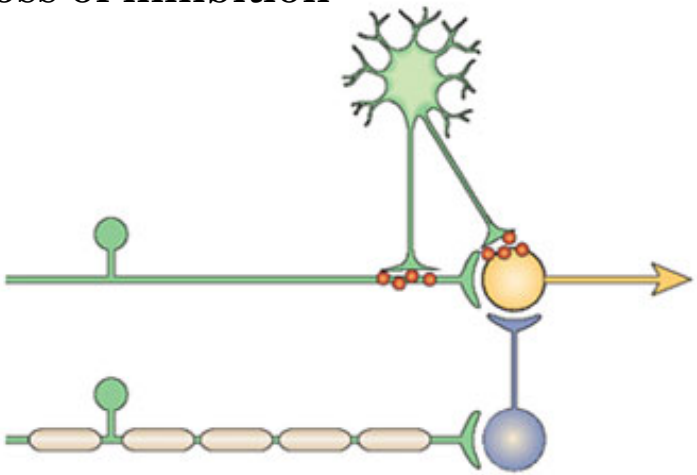
Changes in synaptic connectivity

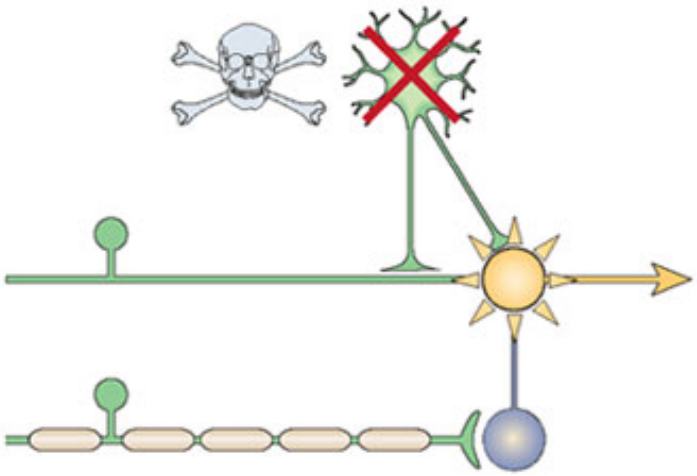


Sprouting after nerve injury



Loss of inhibition

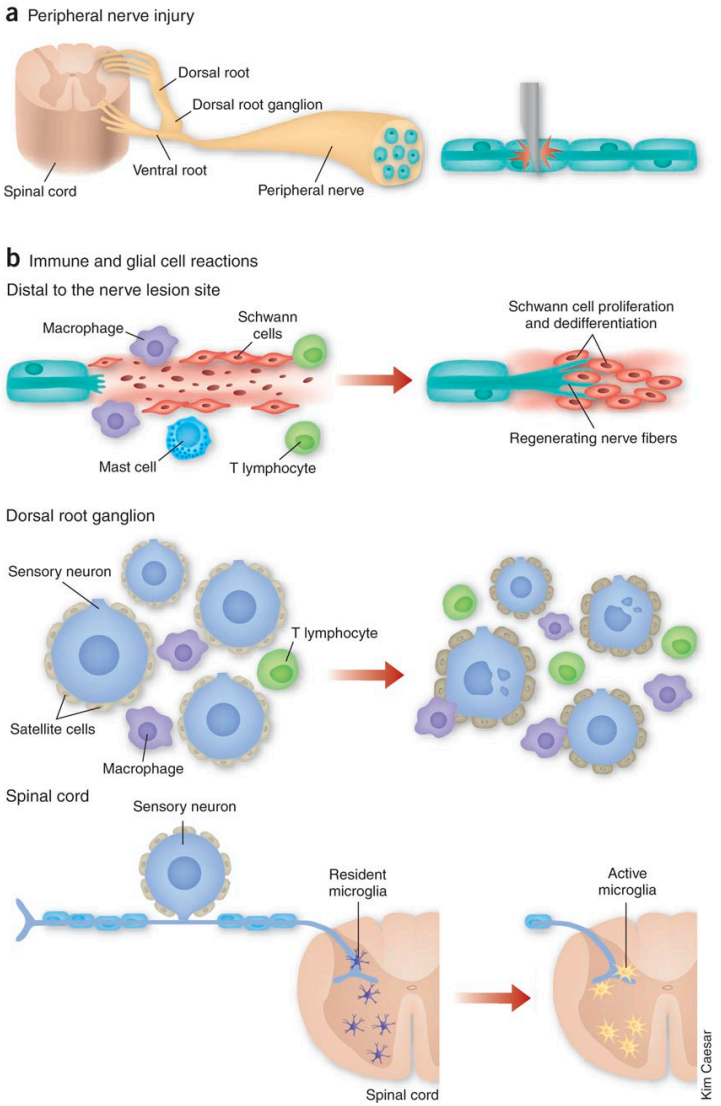




Scholtz J, Woolf CJ. *Nat Neurosci.* 2002;5:1062–1067.

Immune and glial cell reactions

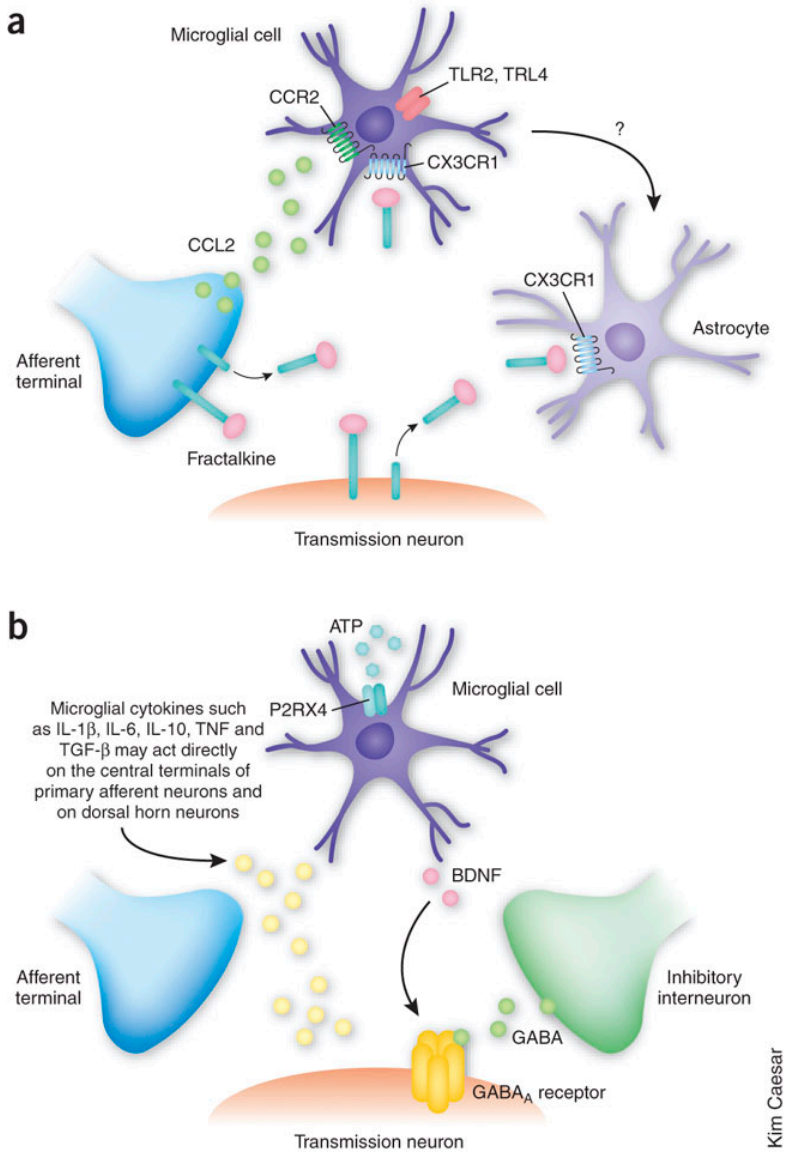
Peripheral nerve injury provokes recruitment and activation of immune cells at the site of nerve lesion, in the DRG and in the spinal cord.



Scholtz J, Woolf CJ. *Nat Neurosci.* 2007, 10:1361-1368.

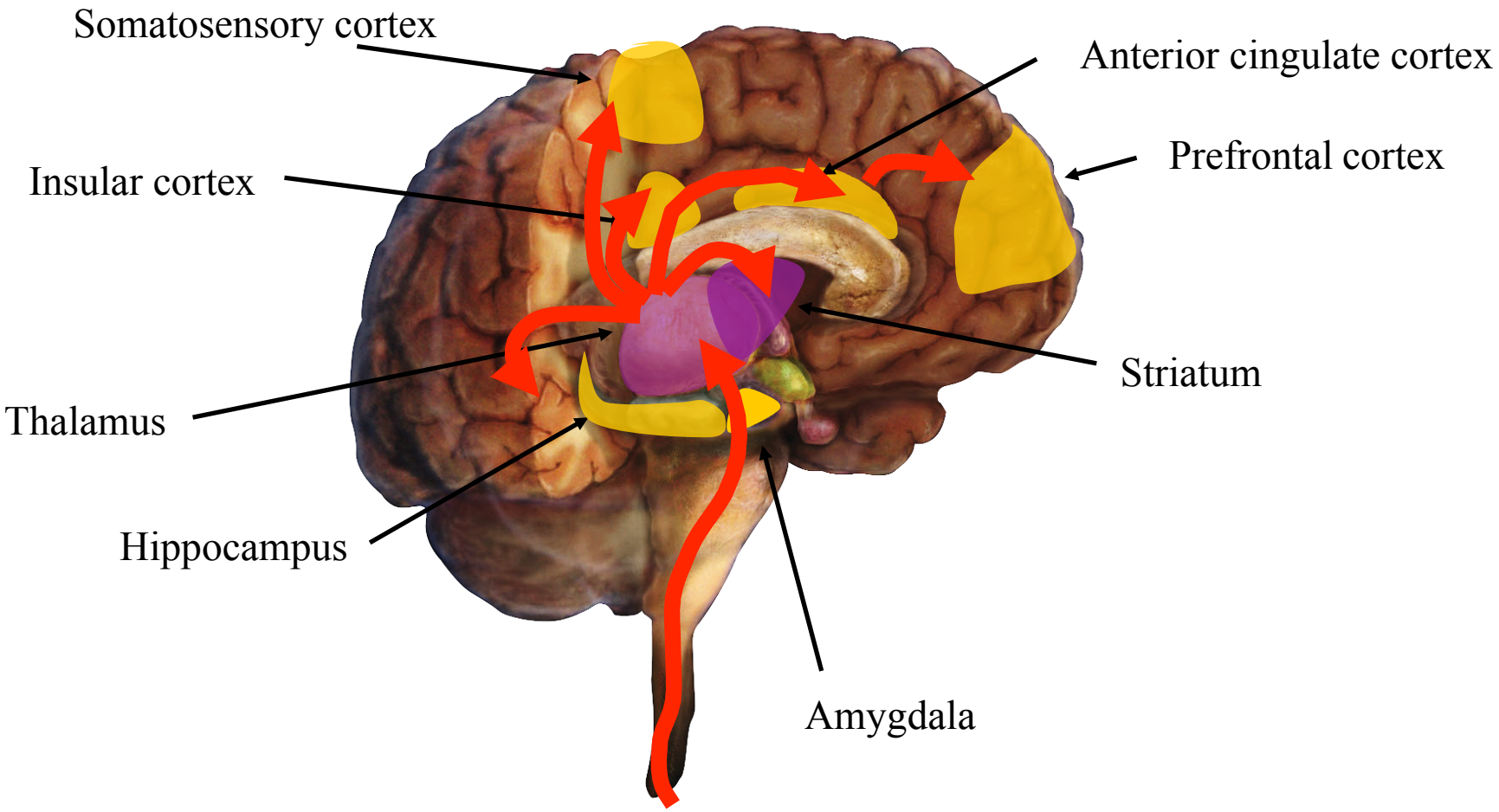
Glial-neuron interactions

Microglial cytokines may act directly on central terminals of primary afferents and dorsal horn neurons.



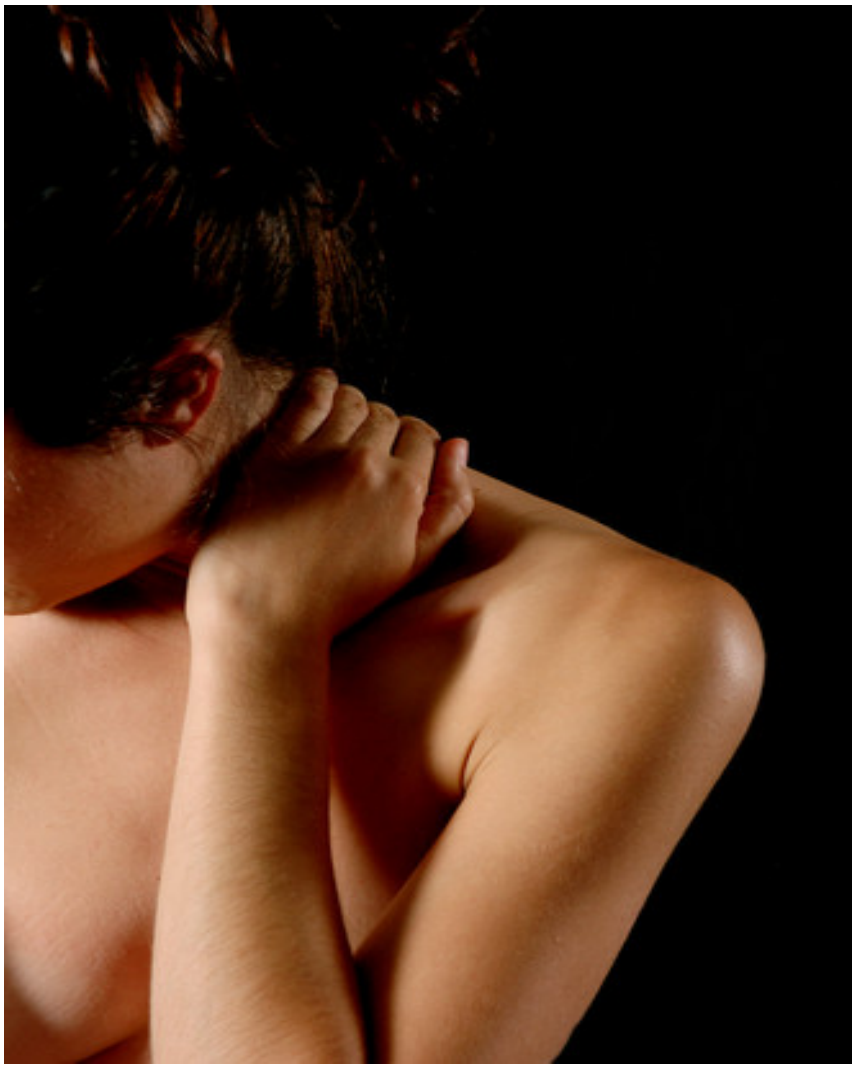
Scholtz J, Woolf CJ. *Nat Neurosci.* 2007, 10:1361-1368.

Central pain processing and modulation changes can occur at supraspinal levels

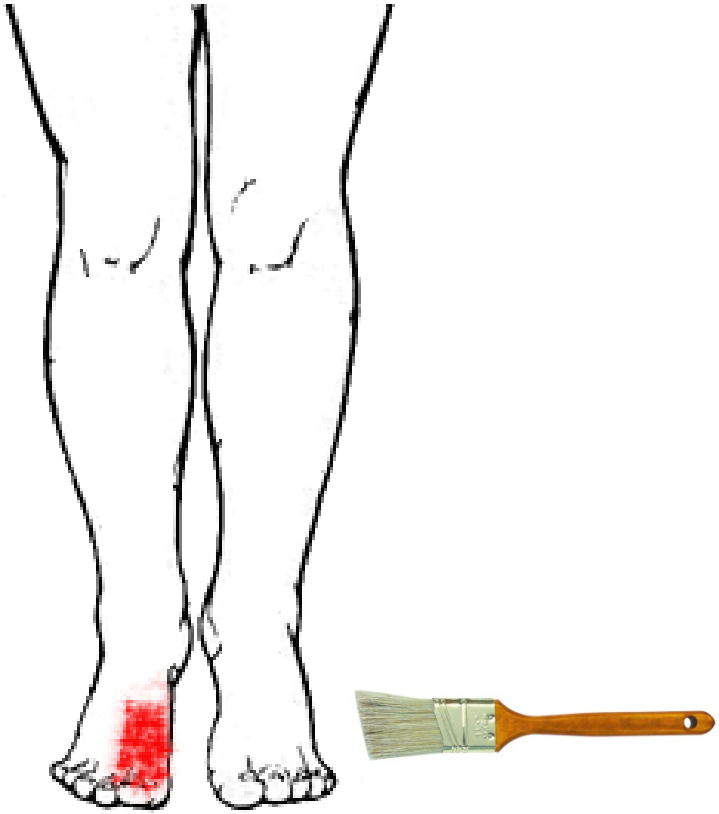


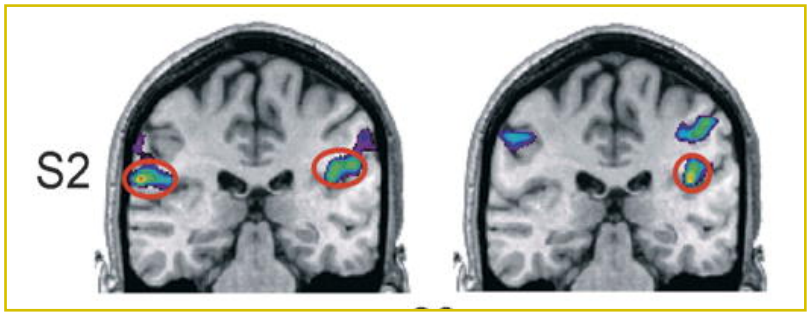
Adapted from Apkarian et al. *Eur J Pain* 2005;9(4):463-84

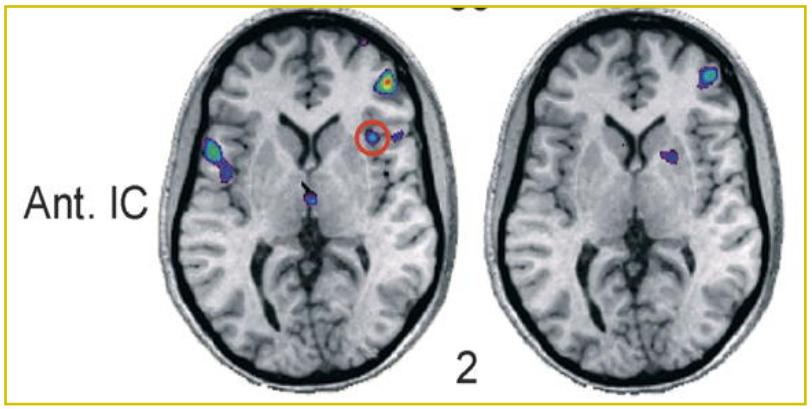
Evidence for enhanced pain processing in chronic pain disorders

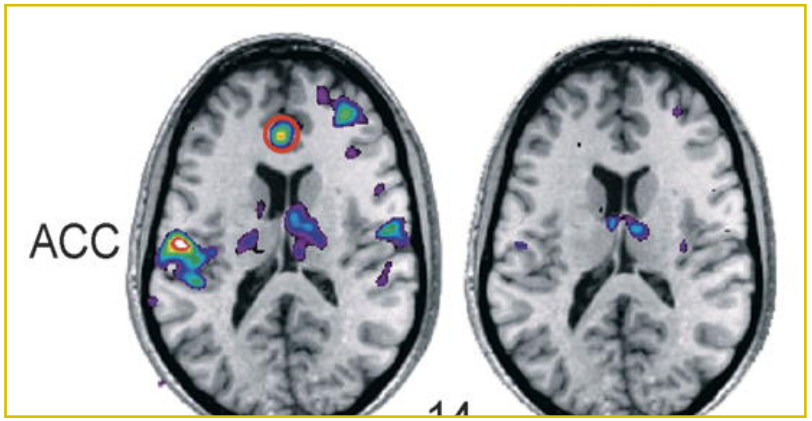


Allodynia related to neuropathic pain is reflected in brain



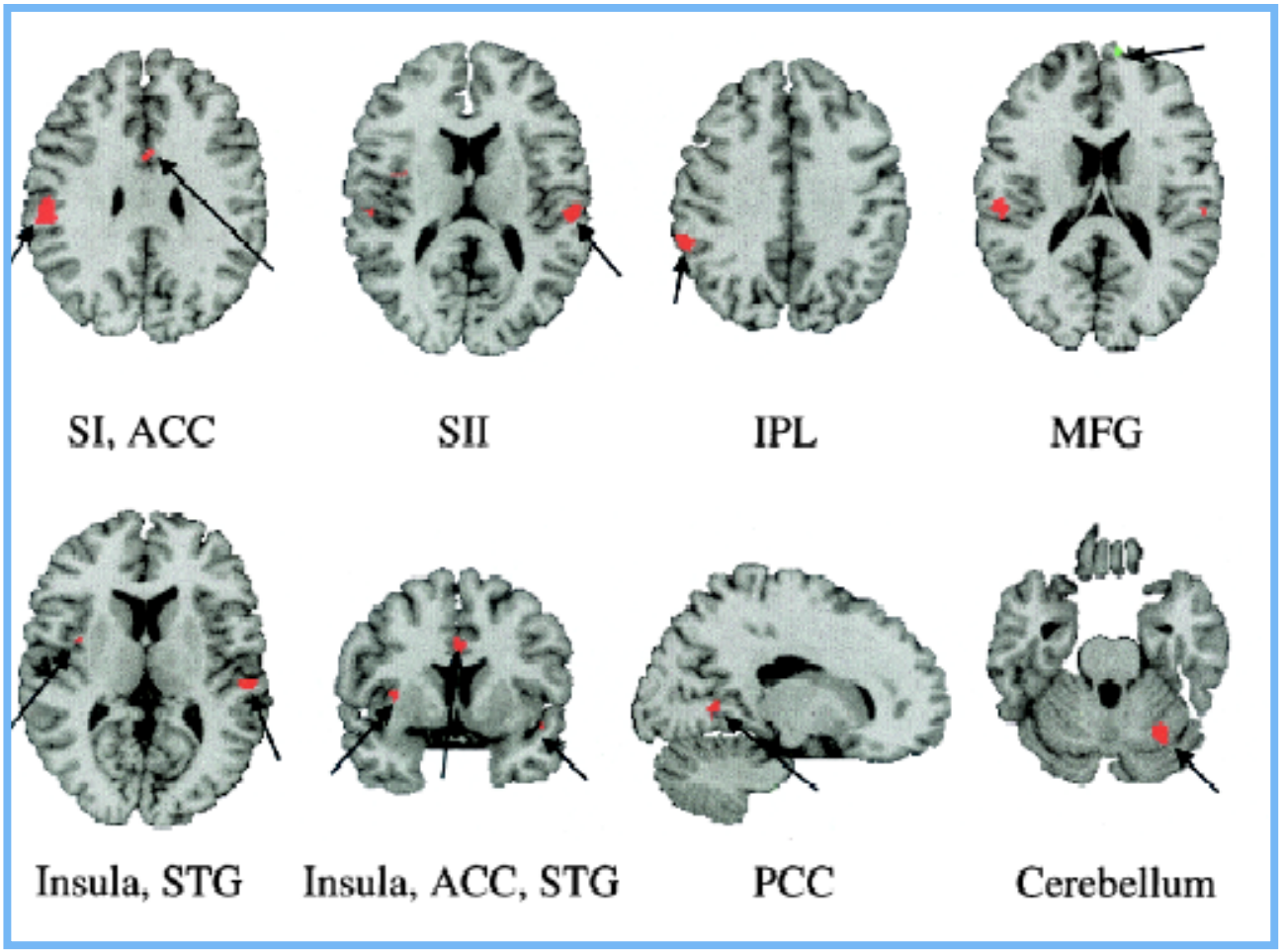


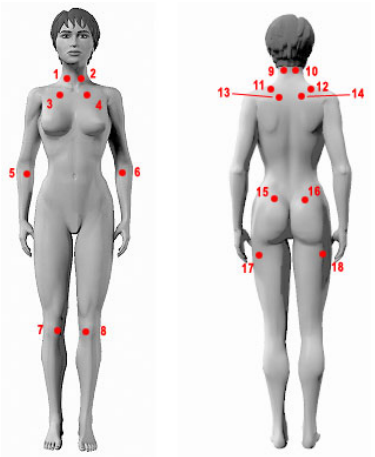


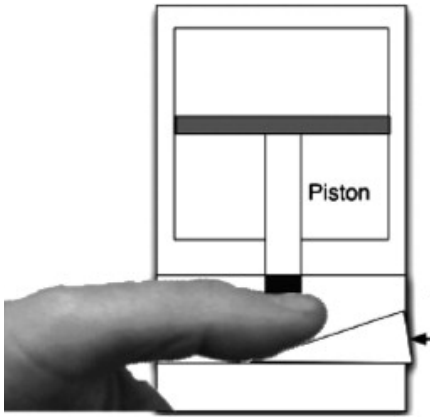


ACC: Anterior cingulate cortex; Ant: Anterior; IC: Insular cortex.
Hofbauer RK, et al. *Clin J Pain*. 2006;22:104–108.

Increased activation to pressure with fibromyalgia

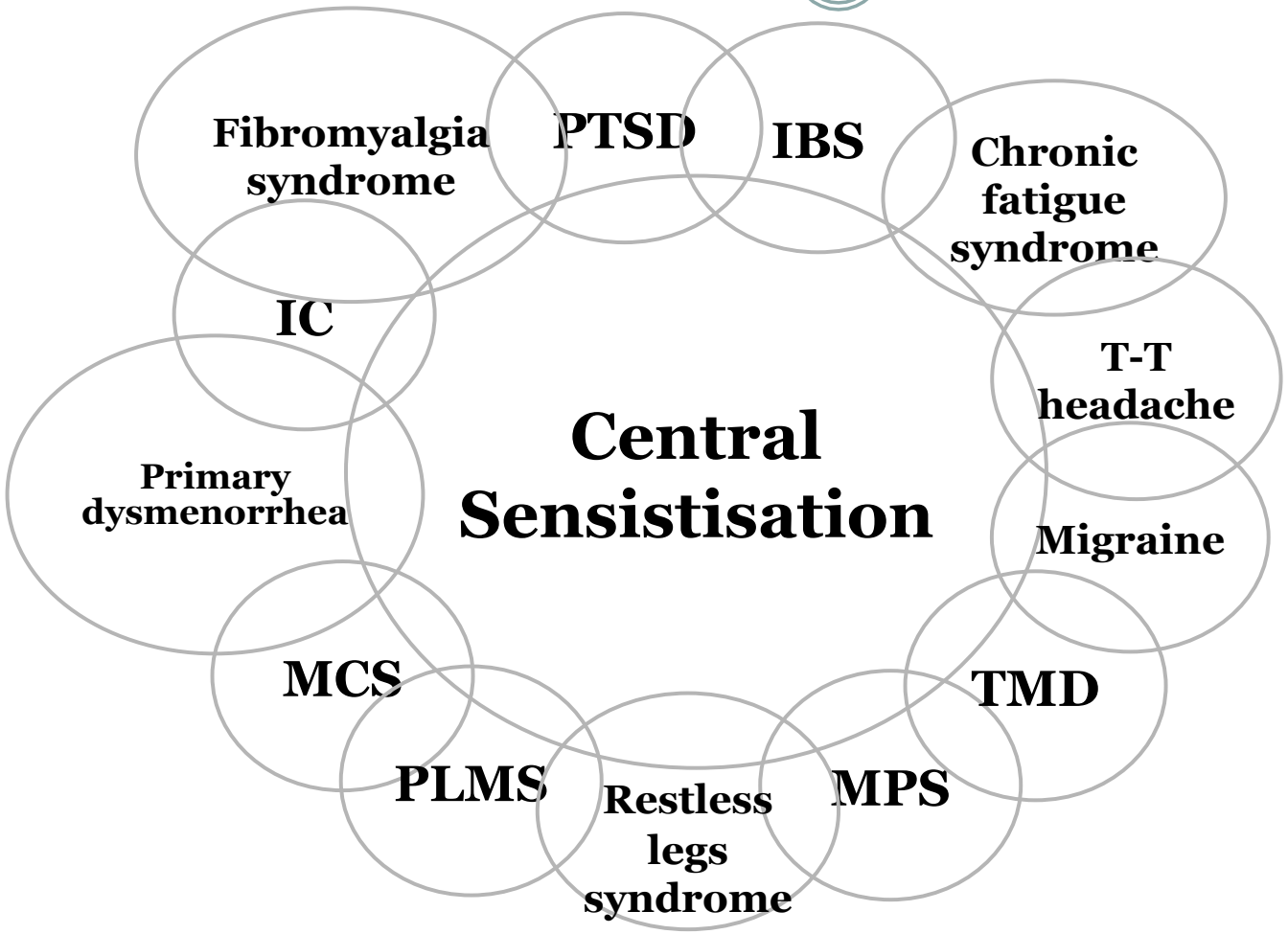




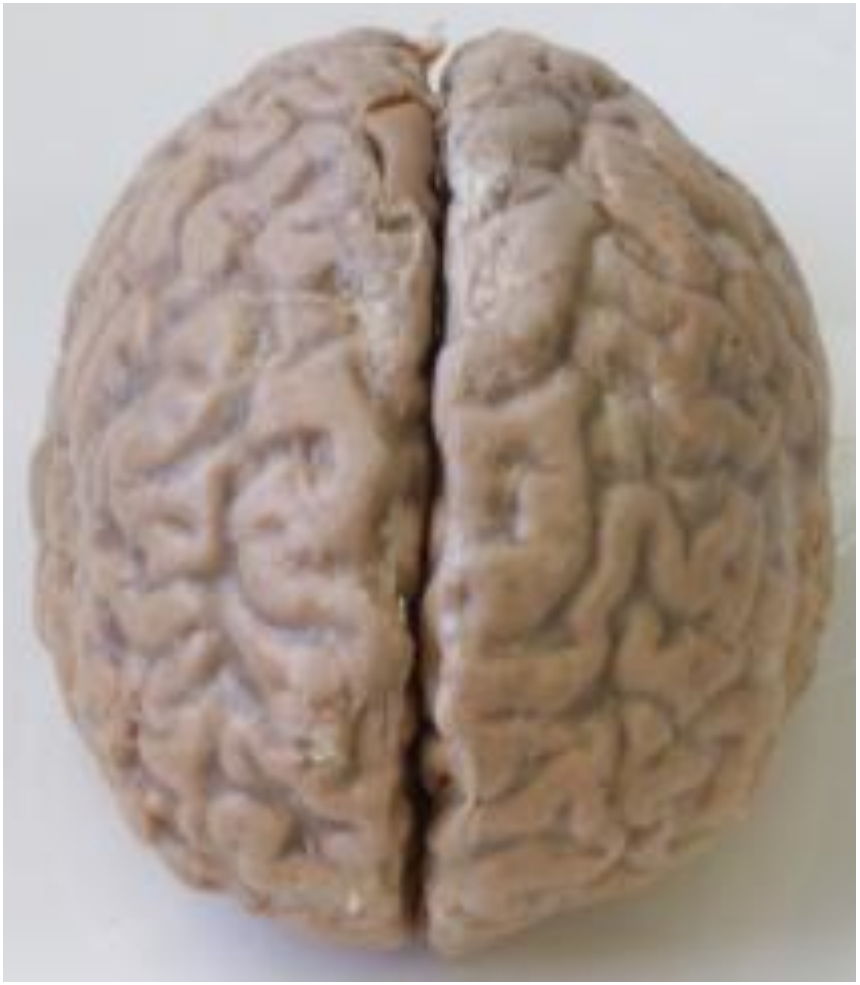


Gracely et al 2002

Central sensitization may play a key role in many pathological pain conditions



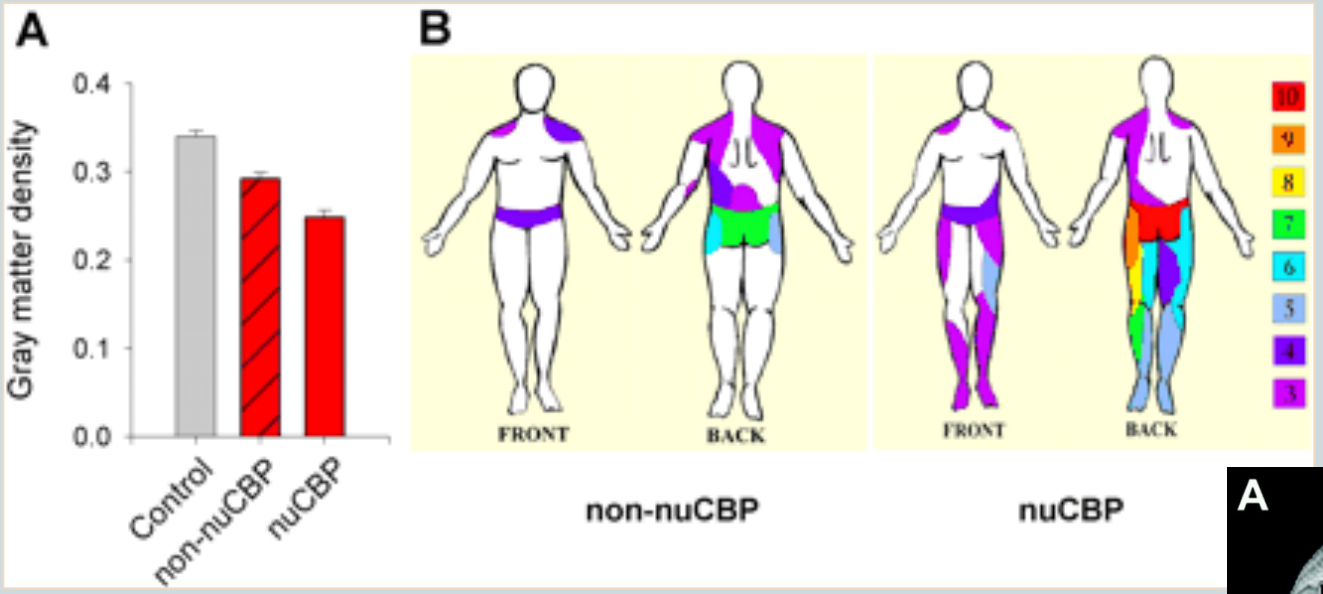
IBS=Irritable bowel syndrome;
IC=Interstitial cystitis;
MCS=Multiple chemical sensitivity;
MPS=Mucopolysaccharidosis;
PLMS=Periodic limb movements in sleep;
PTSD=Post-traumatic stress disorder;
TMD=Temporomandibular disorder;
T-T headache=Tension-type headache.

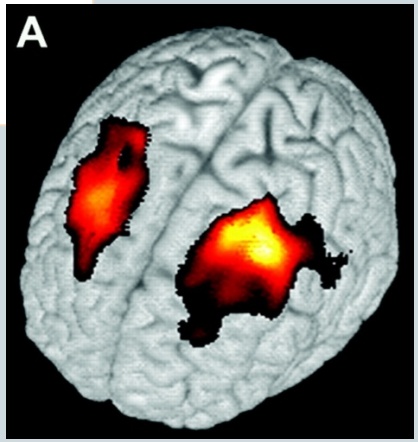


Chronic pain patients have changes in brain gray matter that might reflect changes in pain modulation[1–3]

1. Apkarian AV, et al. *J Neurosci*. 2004;24:10410–10415. 2. Kuchinad A, et al. *J Neurosci*. 2007;404:1104–1107.
3. Davis KD, et al. *Neurology*. 2008;70:153–154.

Gray matter decreased first shown by Apkarian in back pain patients

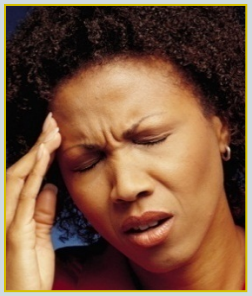


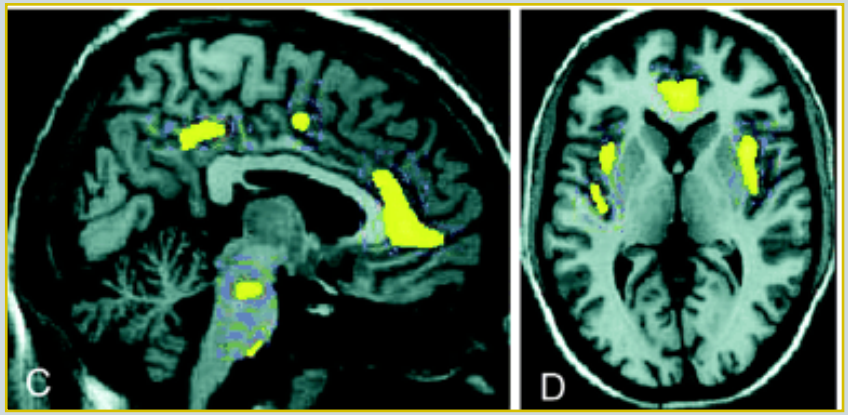


Apkarian AV, et al. *J Neurosci*. 2004;24:10410–10415.

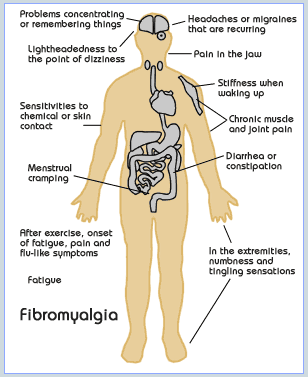
Similar findings with multiple chronic pain conditions

Gray matter decreases in chronic tension-type headache

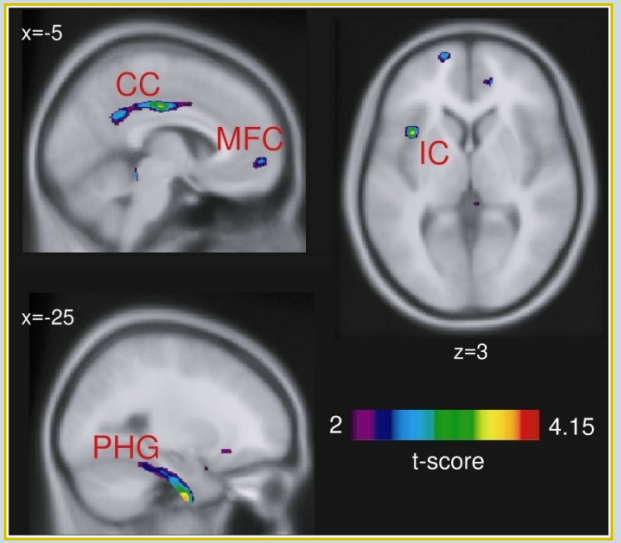




Schmidt-Wilcke T, et al. *Neurology*. 2005;66:1483–1486.

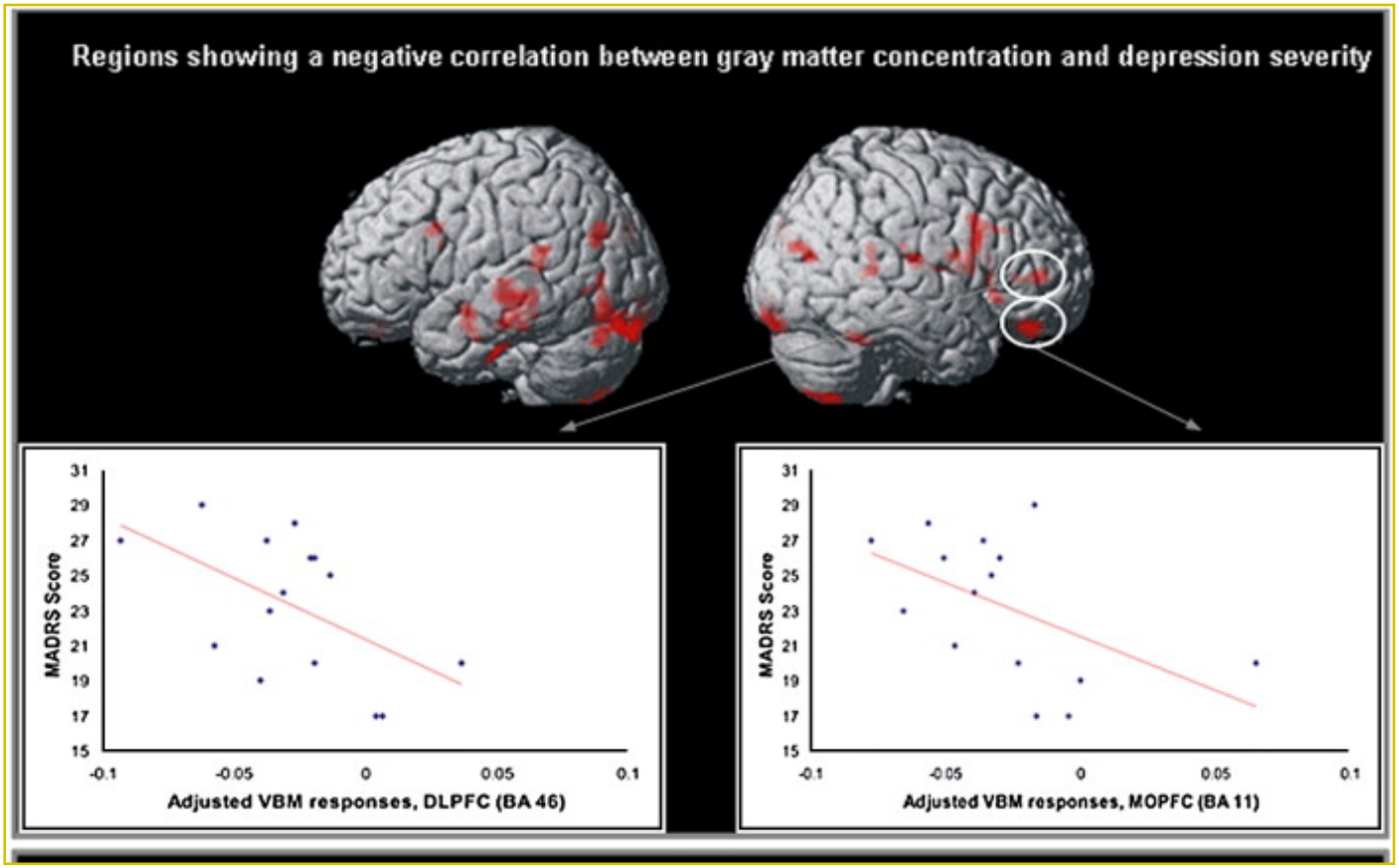


Gray matter decreases in fibromyalgia



Kuchinad A, et al. *J Neurosci*. 2007;404:1104–1107.

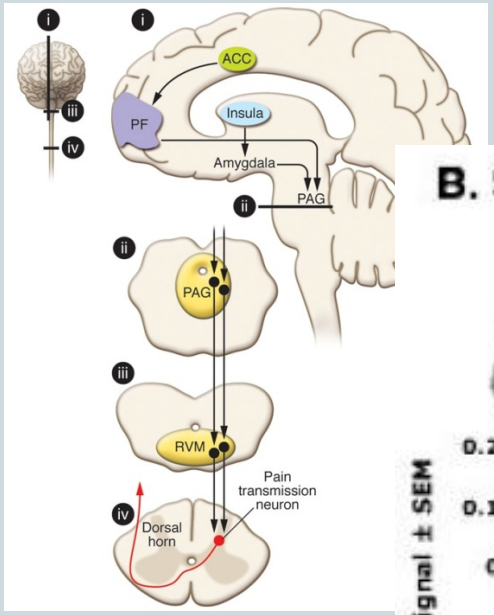
Similar gray matter changes in a variety of mood-related disorders

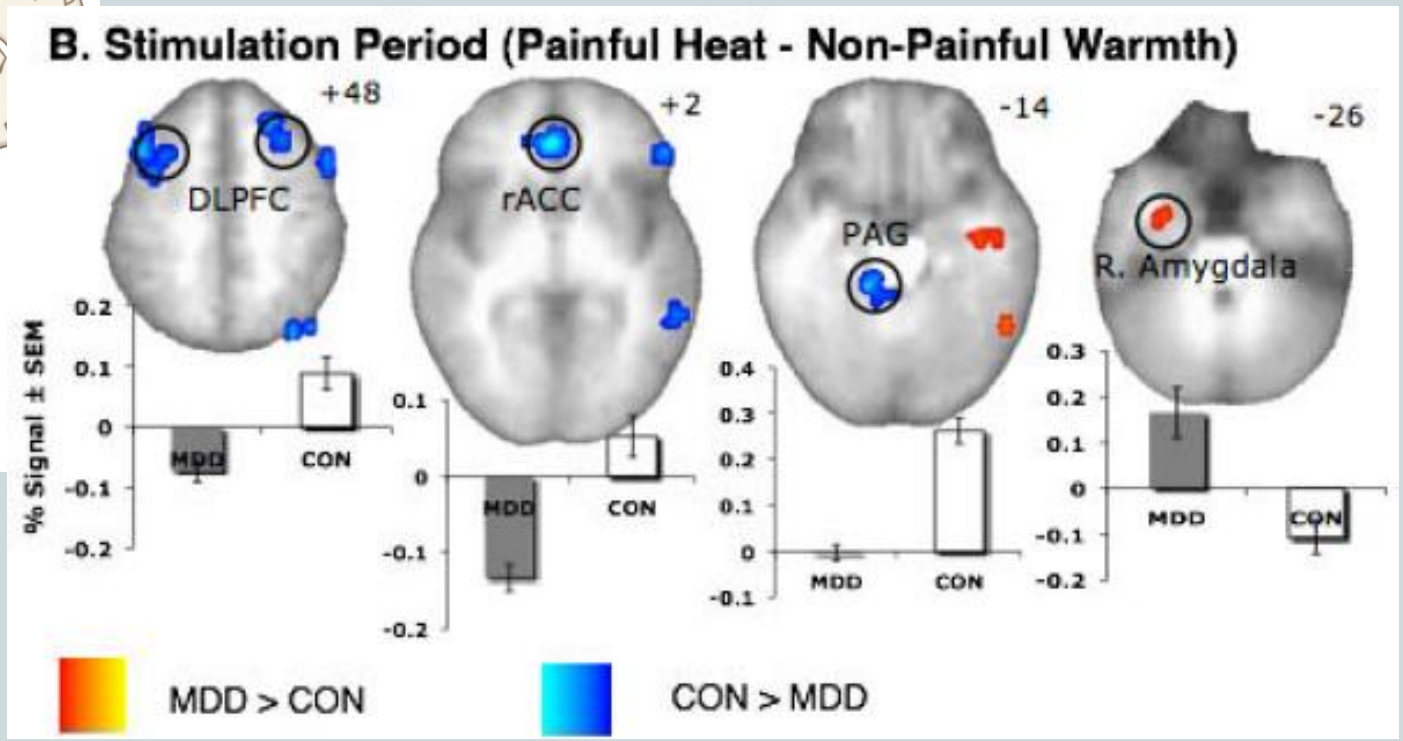


Depression

DLPFC: Dorsolateral prefrontal cortex; MOPFC: Medial and orbital prefrontal cortex.
Vasic N, et al. *J Affect Disord.* 2008;109:107–116.

Major depressive disorder associated with altered descending inhibition during pain

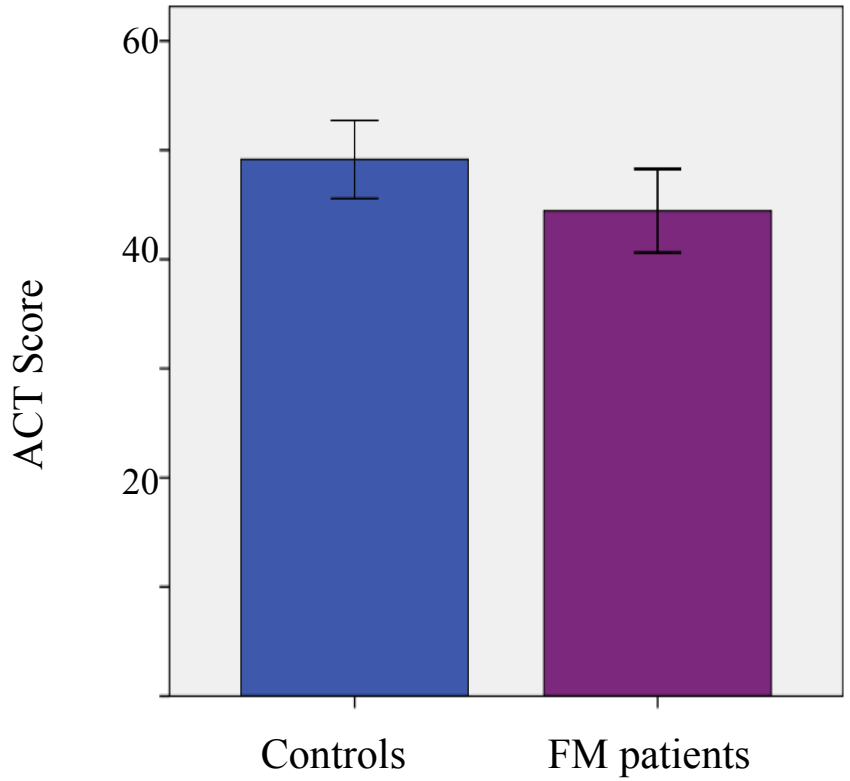


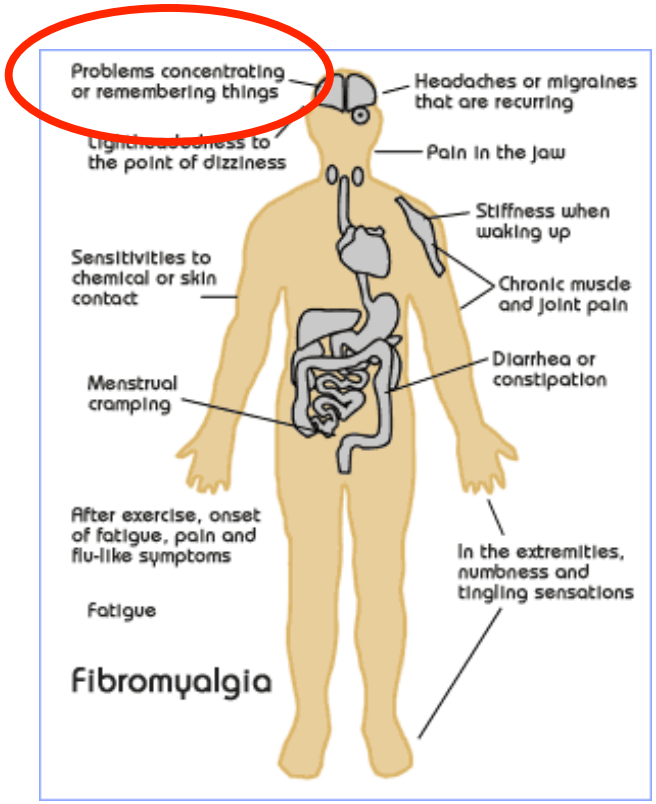


Strigo I et al, Arch Gen Psychiatry 65: 1275-1284, 2008.

What is the emotional/cognitive impact of brain changes in chronic pain?

Working memory worse for FM patients

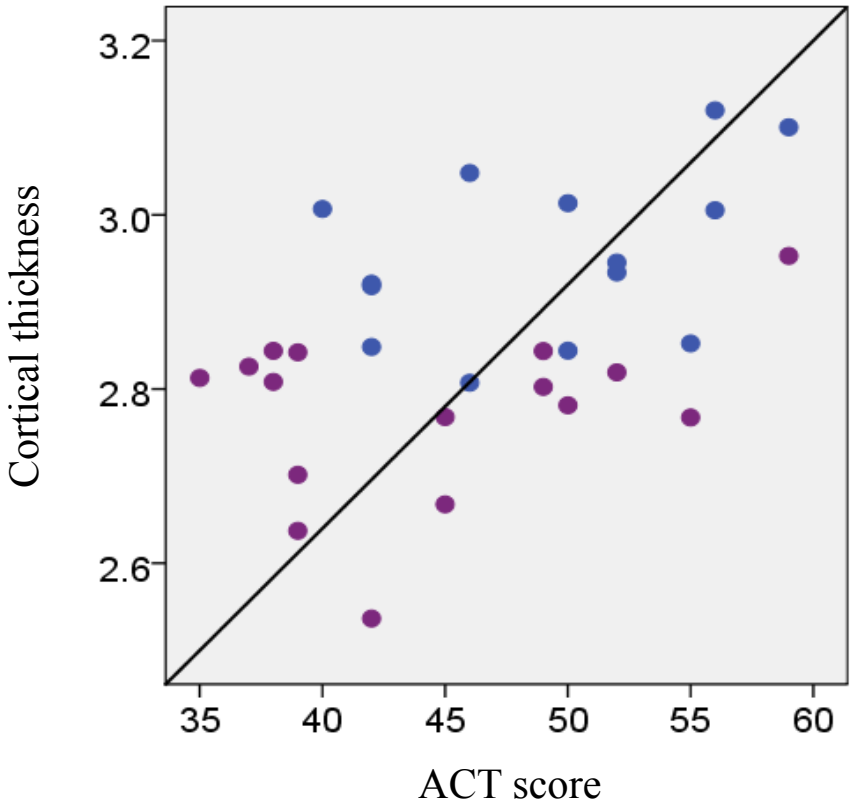


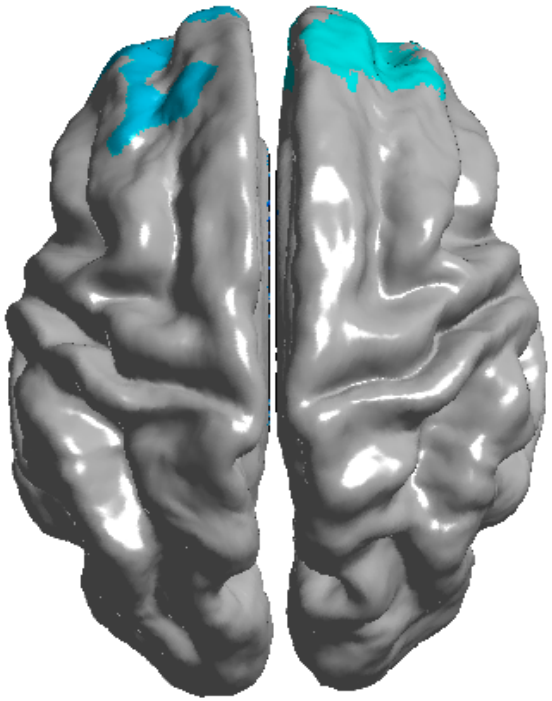


ACT test for working memory during distraction

Ceko et al 2010

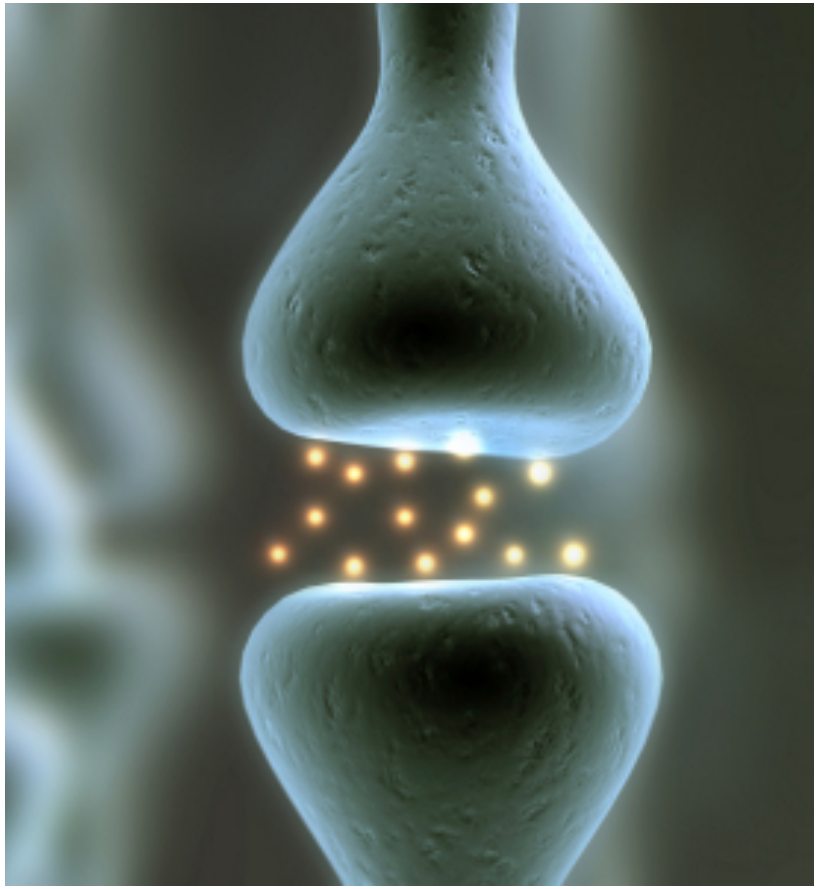
Working memory correlates with frontal cortex thickness



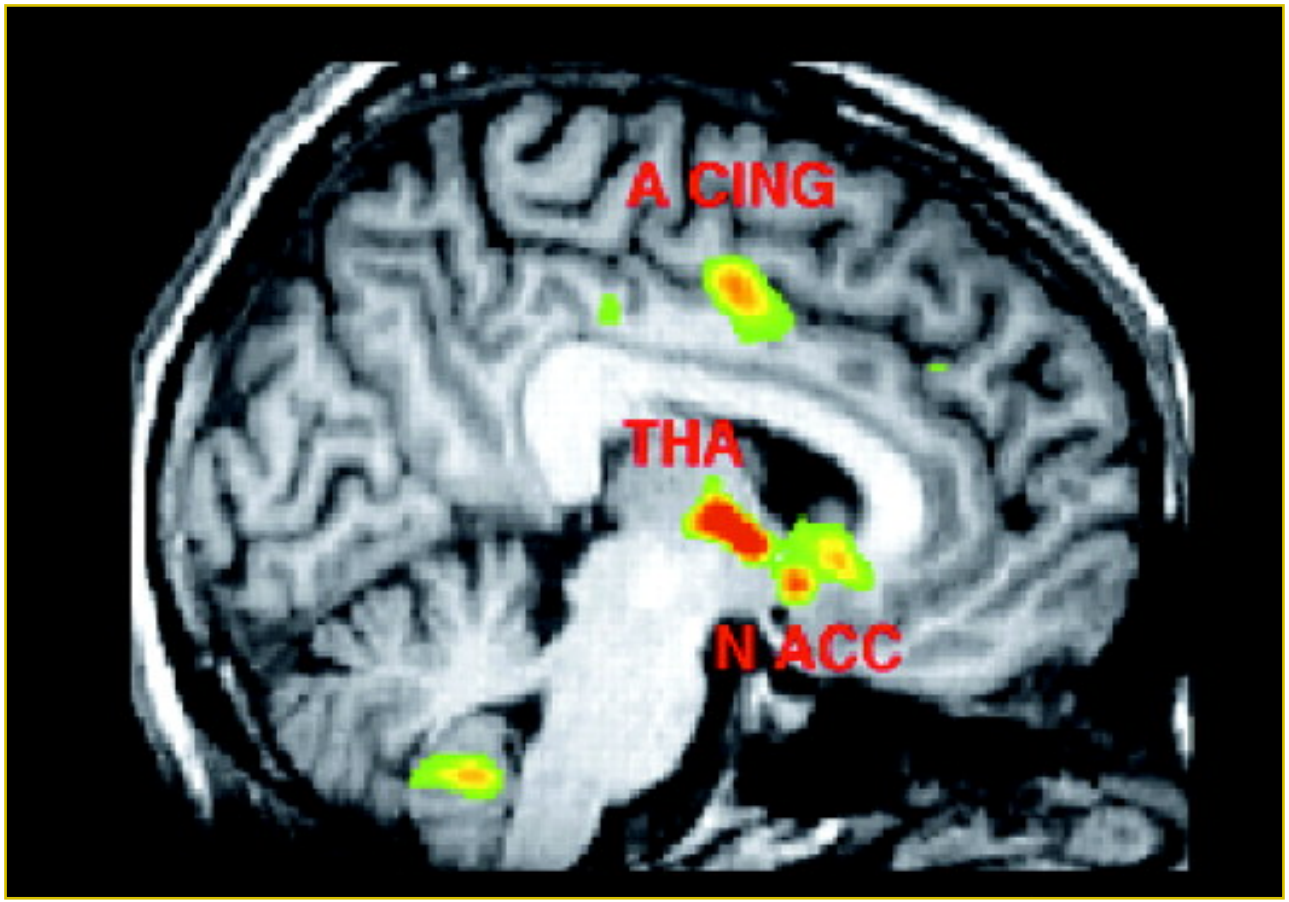


Ceko et al 2010

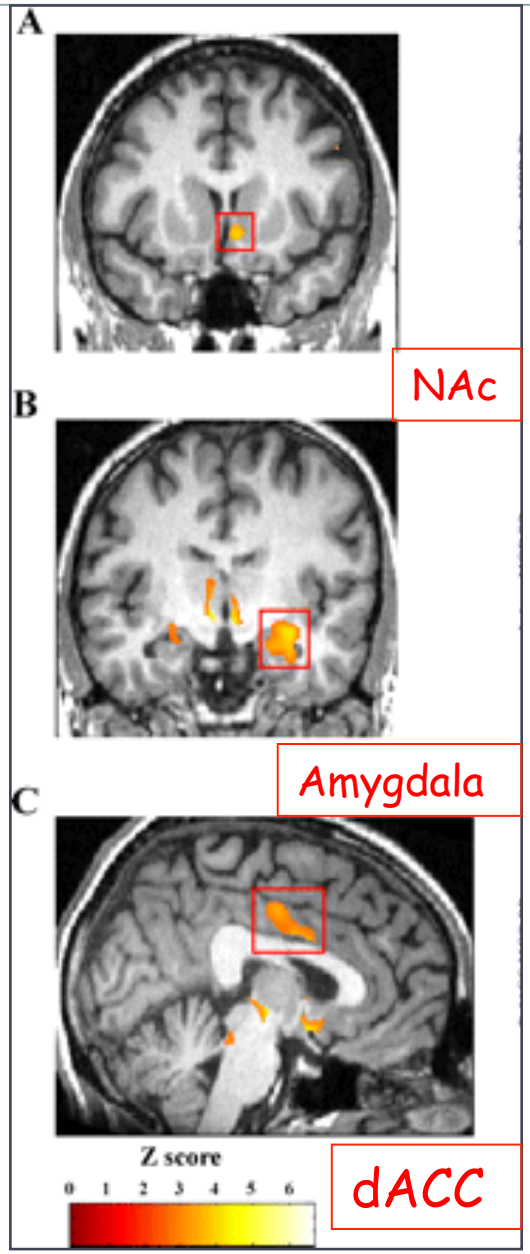
Some chronic pain patients show changes in forebrain neurotransmitter systems



Pain-related opiate binding in cingulate cortex, thalamus and nucleus accumbens



A CING: Anterior cingulate; N ACC: Nucleus accumbens; THA: Thalamus.
Zubieta J-R, et al. *Science*. 2001;293:311–315.



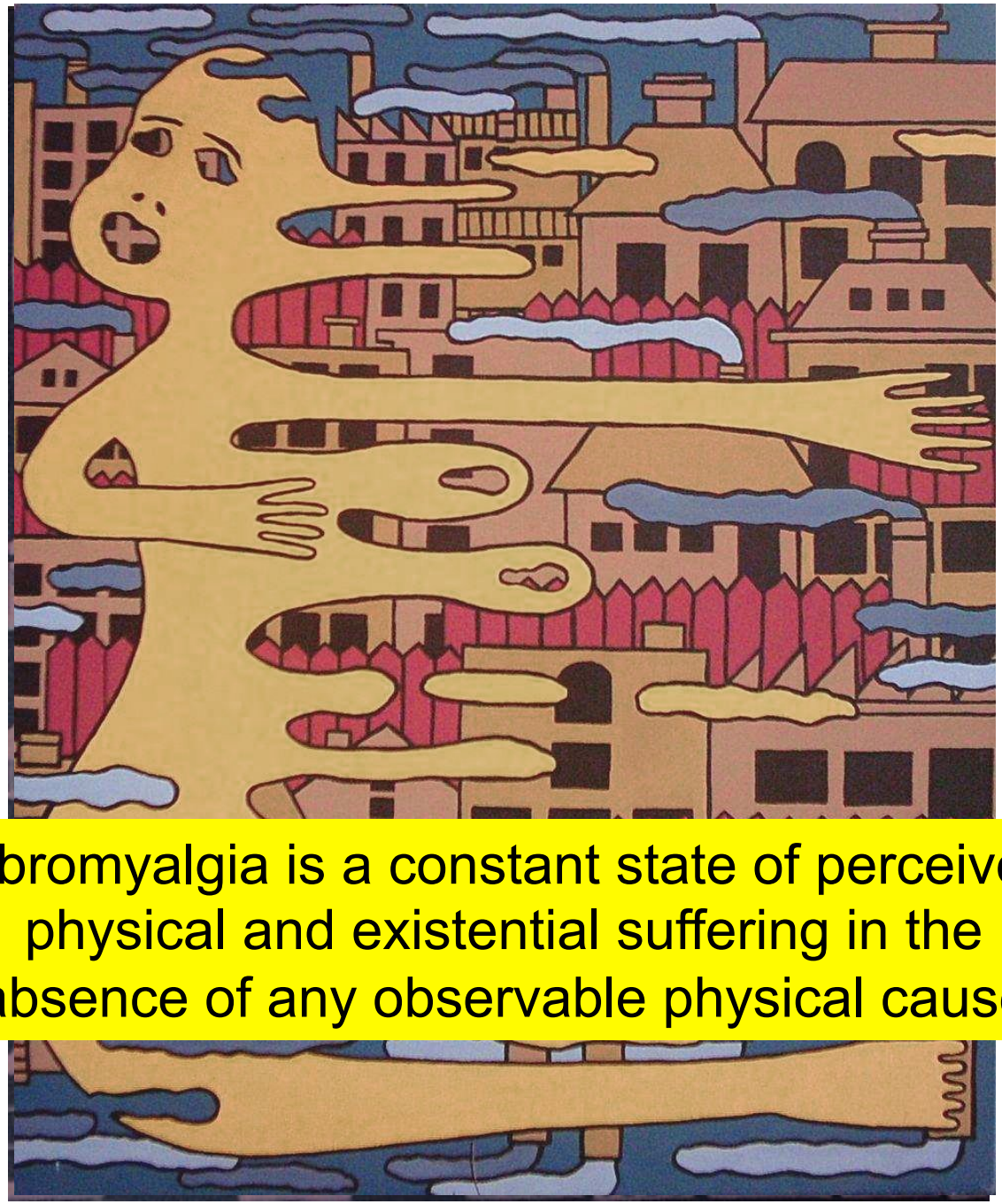
Fibromyalgia patients have reduced μ-opioid binding potential in pain-related brain regions

dACC: Dorsal anterior cingulate; NAc: Nucleus accumbens.
Harris RE, et al. *J Neurosci.* 2007;27:1000–1006.

Conclusions

- Pain is a multidimensional experience that can be transformed from adaptive to a disease state.
- Pain transmission involves peripheral, spinal, and forebrain processing; pain perception is modulated from descending pathways that may have either facilitatory or inhibitory effects.
- Psychological state can have a profound effect on pain perception and associated neural activation.
- Neuroplastic alterations in the CNS can result in sensitization and an imbalance between modulatory descending facilitatory and inhibitory pathways.
- Long-term pain can alter brain anatomy and associated emotions and cognitive function.
- Chronic pain patients may have alterations in forebrain opioid systems

There are 3 levels of pain:
Pain, excruciating pain, and
stepping on a Lego.



Fibromyalgia is a constant state of perceived physical and existential suffering in the absence of any observable physical cause

Non-Musculoskeletal Fibromyalgia Symptoms	Frequency (mean)	Frequency (range)
Fatigue	86%	75-92%
Non-restorative sleep	78%	75-80%
Paresthesia	54%	26-74%
Self-report anxiety	62%	48-72%
Self-report depression	34%	31-37%
Memory decline	70.2%	
Mental confusion	56.1%	
Speech difficulty	40.4%	
Headaches	53%	44-56%
Dysmenorrhea	43%	40-45%
Irritable Bowel Syndrome	40%	30-53%
Restless leg syndrome	31%	
Sicca	15%	12-18%
Female urethral syndrome	12%	

Yunus, et al. Semin Arthritis Rheum. 1981 Aug;11(1):151-71.

1) Widespread Pain Index (WPI): Note the number areas in which the patient has had pain over the last week. In how many areas has the patient had pain?

□ Shoulder Girdle, Lt
□ Upper Arm, Lt
□ Lower Arm, Lt
□ Hip (buttock, trochanter), Lt
□ Upper Leg, Lt
□ Lower Leg, Lt
□ Jaw, Lt
□ Chest
□ Upper Back
□ Neck

□ Shoulder Girdle, Rt.
□ Upper Arm, Rt
□ Lower Arm, Rt
□ Hip (buttock, trochanter), Rt
□ Upper Leg, Rt
□ Lower Leg, Rt
□ Jaw, Rt
□ Abdomen
□ Lower Back

WPI Score (0 – 19): _____

2a) Symptoms Severity Score (SS): Patient Impression

For the each of the three symptoms below, indicate the level of severity over the **past week** using the following scale:

0 = No problem
1 = Slight or mild problems; generally mild or intermittent
2 = Moderate; considerable problems; often present and/or at a moderate level
3 = Severe: pervasive, continuous, life-disturbing problems

Fatigue (0 – 3): _____
Waking unrefreshed (0 – 3): _____
Cognitive symptoms (0 – 3): _____

2b) Symptoms Severity Score (SS): Physician Impression

Considering somatic symptoms in general, indicate whether the patient has:

0 = No symptoms
1 = Few symptoms
2 = A moderate number
3 = A great deal of symptoms

Physician Impression Score (0 – 3): _____

Total Symptoms Severity Score (SS) (0 – 12): _____
Fibromyalgia Severity Score (0 – 31): _____
Fibromyalgia Severity Score = WPI score + SS score

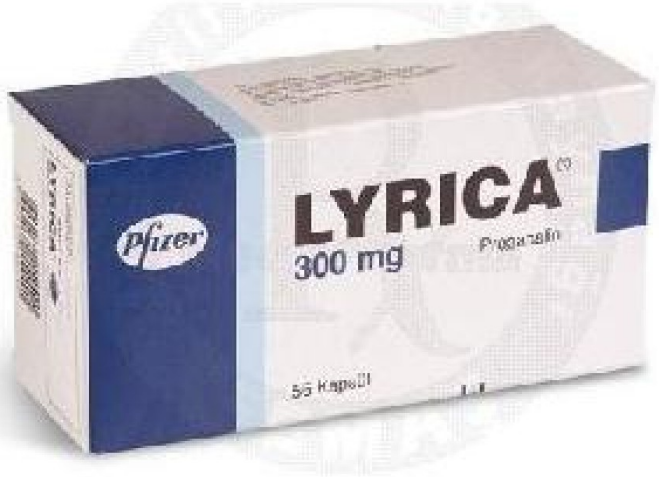
Meets 2010 ACR Criteria:
□ **Yes** (*WPI ≥ 7 and SS ≥ 5)*
□ **Yes** (*WPI = 3-6 and SS ≥ 9)*
□ **No**

The fibromyalgia concept has evolved from the archetypal functional pain disorder to a multi-symptom disorder in which pain is only one, if not the most prominent, of many symptoms.

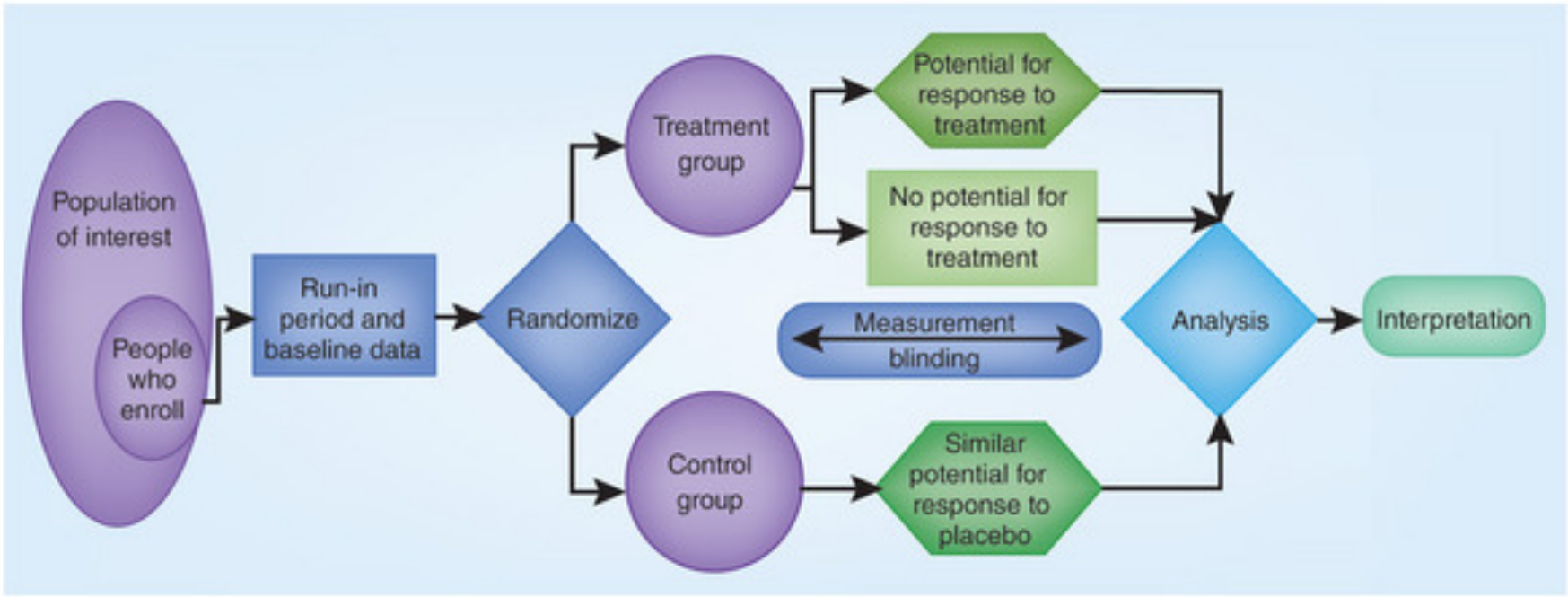
Central sensitization is an “increase in the excitability of the central nervous system so that normal inputs now evoke exaggerated responses”.

Can we successfully treat fibromyalgia by medically altering central sensitization?

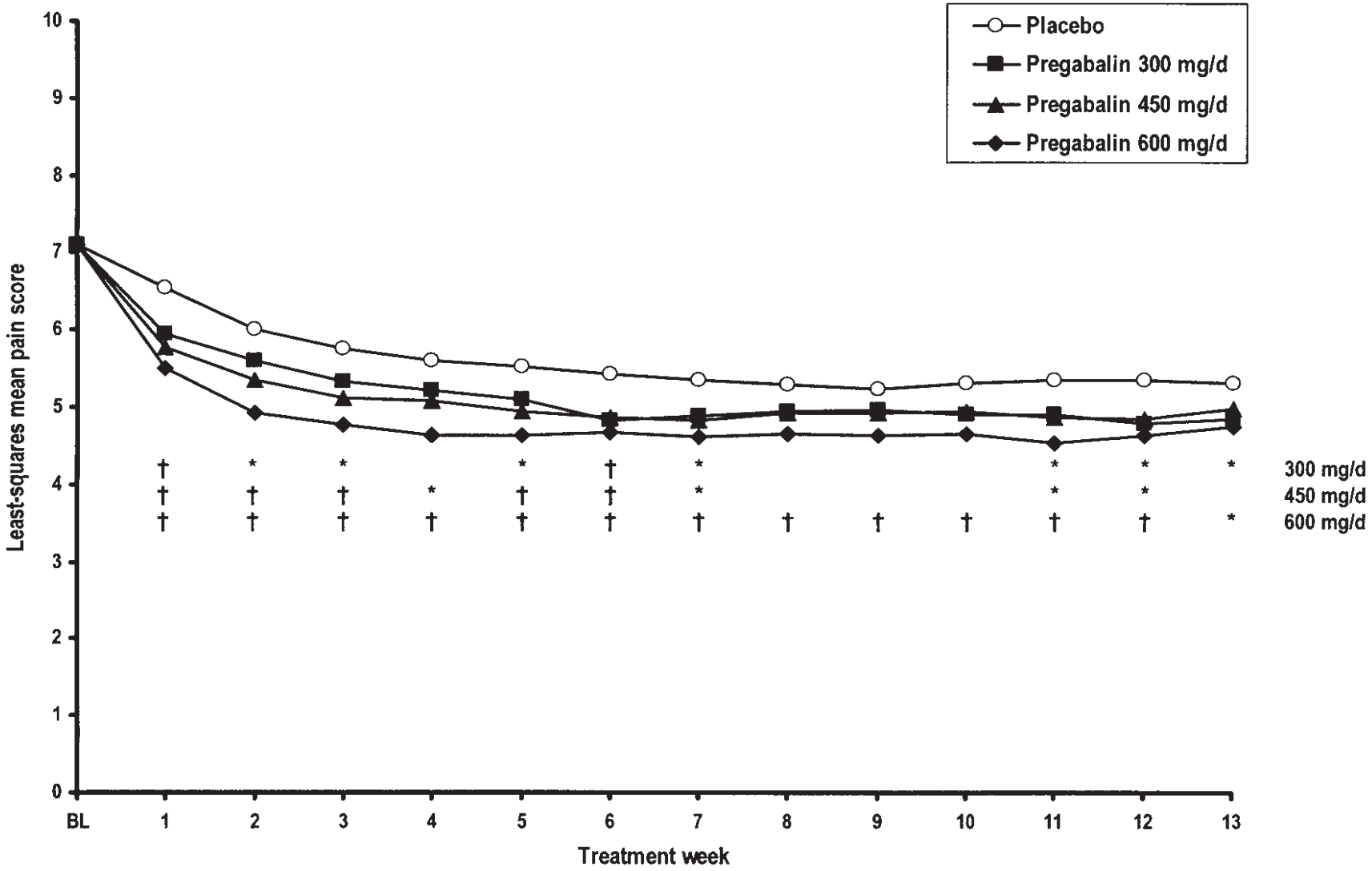
DRUGS FOR FIBROMYALGIA PAIN



Double Blind Placebo Controlled Trials

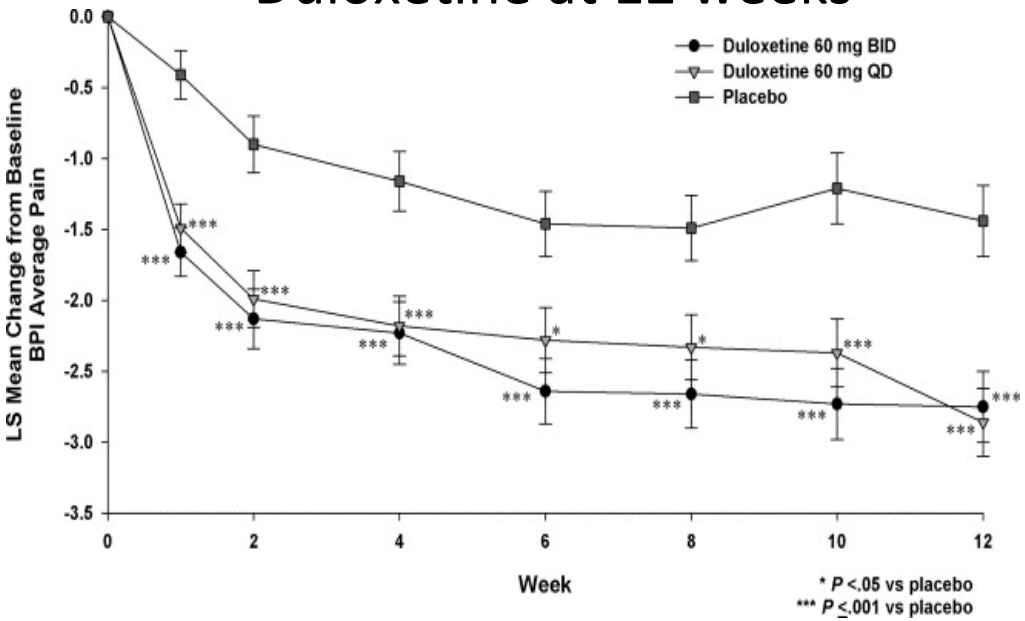


Pregabalin at 13 weeks



A Randomized, Double-blind, Placebo-Controlled, Phase III Trial of Pregabalin in the Treatment of Patients with Fibromyalgia: PHILIP J. MEASE, I. JON RUSSELL, LESLEY M. ARNOLD, HANA FLORIAN, JAMES P. YOUNG Jr, SUSAN A. MARTIN, and UMA SHARMA

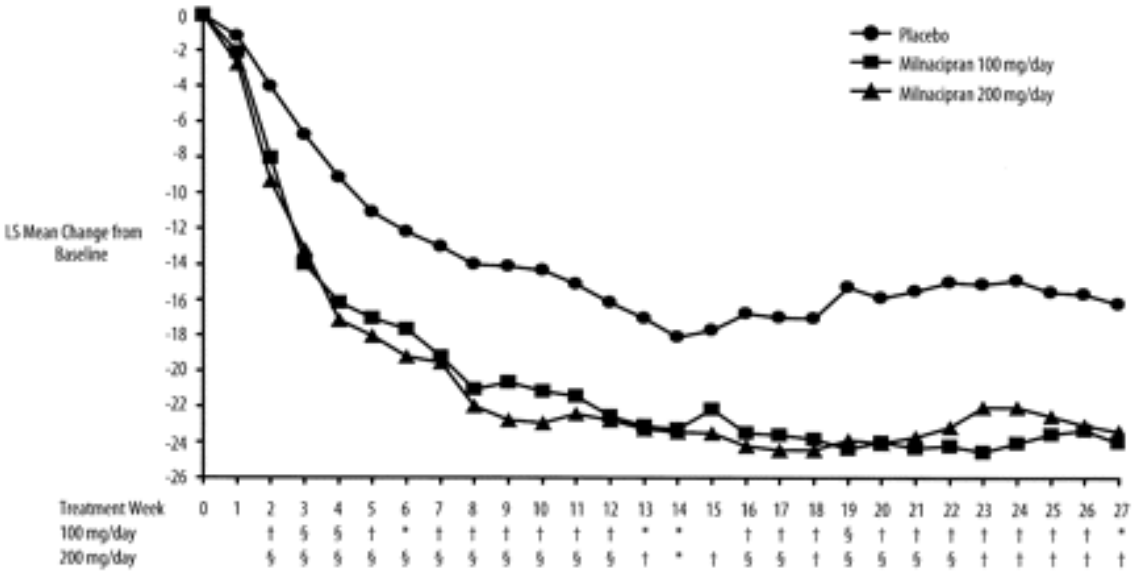
Duloxetine at 12 weeks



A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. Arnold LM, Rosen A, Pritchett YL, D'Souza DN, Goldstein DJ, Iyengar S, Wernicke JF Pain. 2005 Dec 15;119(1-3):5-15.

FDA Approved

Milnacipran at 3 months



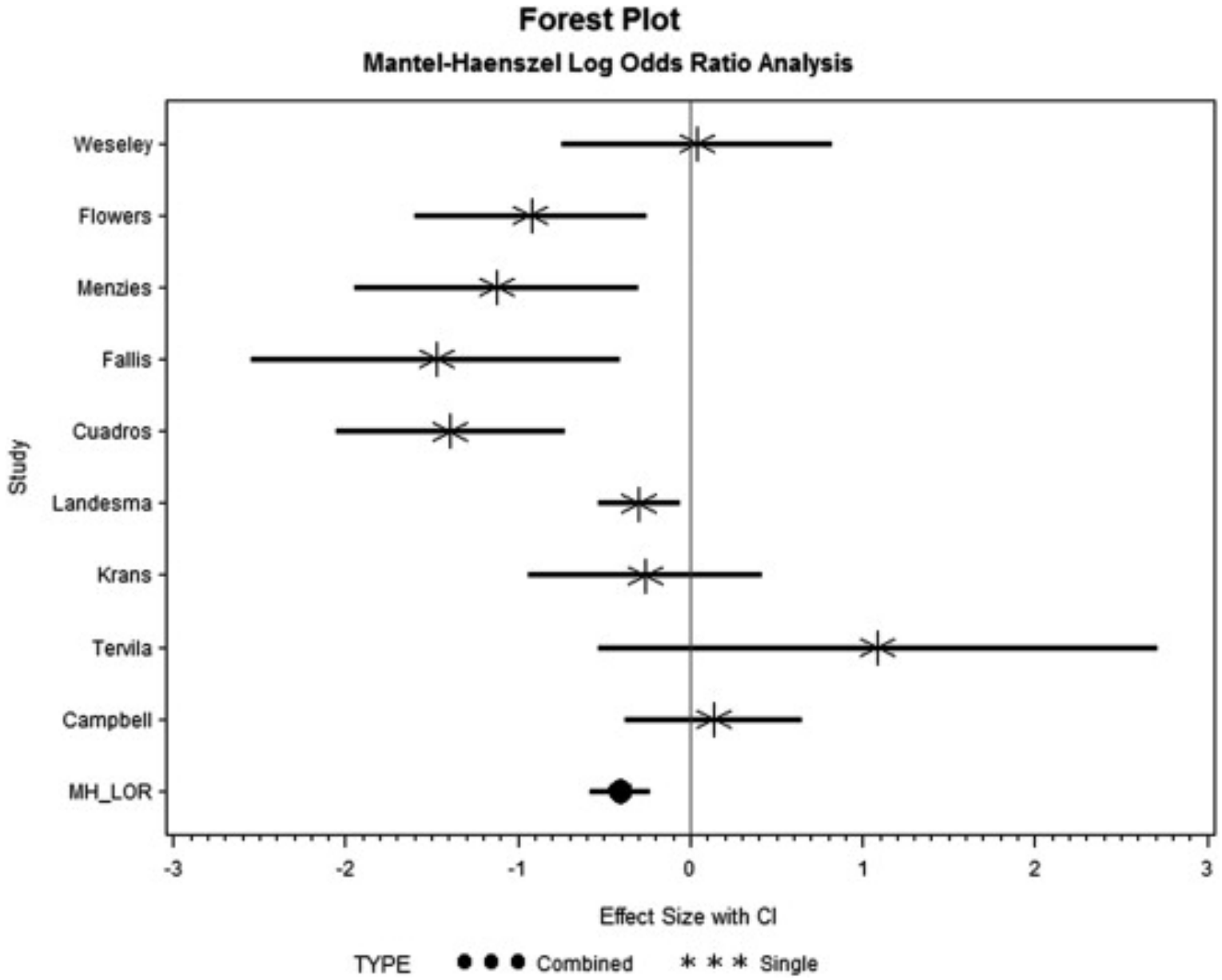
The efficacy and safety of milnacipran for treatment of fibromyalgia. a randomized, double-blind, placebo-controlled trial. Mease PJ, Clauw DJ, Gendreau RM, Rao SG, Kranzler J, Chen W, Palmer RH.J Rheumatol. 2009 Feb;36(2):398-409.

~$253.4 million on fibromyalgia medication advertising in Q1-3 in 2008

~$307 million in fibromyalgia sales for pregabalin (2007-2008)

~$279 million in fibromyalgia sales for duloxetine (2007-2008)

(Datamonitor 2009)


Forest Plot
Mantel-Haenszel Log Odds Ratio Analysis
Weseley
Flowers
Menzies
Fallis
Cuadros
Landesma
Krans
Tervila
Campbell
MH_LOR
Study
-3
-2
-1
0
1
2
3
Effect Size with CI
TYPE
Combined
Single

Treatment of fibromyalgia syndrome with gabapentin and pregabalin--a meta-analysis of randomized controlled trials.

Häuser W, Bernardy K, Uçeyler N, Sommer C.

Review: Efficacy of gabapentin and pregabalin in fibromyalgia syndrome (Version 02)
Comparison: 01 Pregabalin and gabapentin versus placebo
Outcome: 01 Pain

Study or sub-category	PGB and GPT N	PGB and GPT Mean (SD)	Placebo N	Placebo Mean (SD)	SMD (random) 95% CI
01 Mean					
Crofford Prega300mg	132	5.60 (2.30)	129	5.80 (2.00)	
Crofford Prega450mg	128	4.90 (2.50)	129	5.80 (2.00)	
Crofford Prega150 mg	131	5.60 (2.00)	129	5.80 (2.00)	
Arnold Gabapentin	57	3.20 (2.00)	62	4.60 (2.60)	
Subtotal (95% CI)	448		449		
Test for heterogeneity: Chi² = 7.84, df = 3 (P = 0.05), I² = 61.7%					
Test for overall effect: Z = 2.45 (P = 0.01)					
02 Mean change					
Arnold Prega 300 mg	183	-1.75 (2.16)	184	-1.04 (2.03)	
Arnold Prega 450 mg	190	-2.03 (2.07)	184	-1.04 (2.03)	
Arnold Prega 600 mg	188	-2.05 (2.06)	184	-1.04 (2.03)	
Mease Prega 300 mg	185	-1.84 (2.17)	190	-1.40 (2.20)	
Mease Prega 450 mg	183	-1.87 (2.17)	190	-1.40 (2.20)	
Measa Prega 600 mg	190	-2.06 (2.20)	190	-1.40 (2.20)	
Pauer Prega 300 mg	183	-1.05 (1.89)	184	-0.72 (1.90)	
Pauer Prega 450 mg	181	-1.26 (1.88)	184	-0.72 (1.90)	
Pauer Prega 600 mg	186	-0.95 (1.91)	184	-0.72 (1.90)	
Subtotal (95% CI)	1669		1674		
Test for heterogeneity: Chi² = 12.43, df = 8 (P = 0.13), I² = 35.6%					
Test for overall effect: Z = 6.66 (P < 0.00001)					

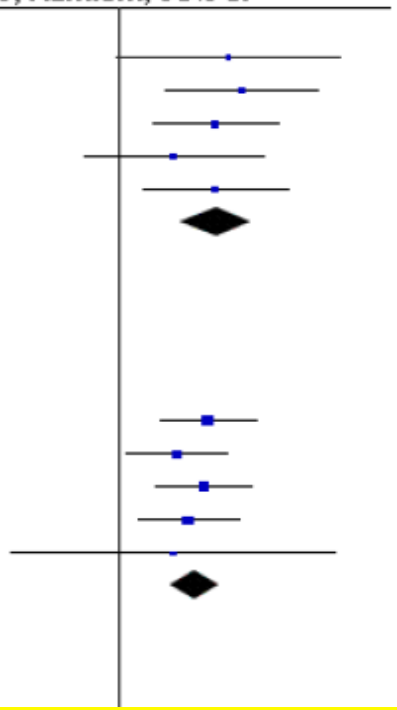
Standard Mean Difference in Pain: -.27 (Cohen's: small effect on pain)
Number Needed to Treat: 12 Number Needed to Harm: 12

[Intervention Review]

Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome

Winfried Häuser[1], Gerard Urrútia[2], Sera Tort[3], Nurcan Üçeyler[4], Brian Walitt[5]

Study or Subgroup	SNRIs Events	SNRIs Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
1.3.1 Duloxetine						
Arnold 2004	29	104	17	103	3.3%	1.69 [0.99, 2.88]
Arnold 2005	95	230	27	118	6.9%	1.81 [1.25, 2.60]
Arnold 2010a	83	249	52	248	10.4%	1.59 [1.18, 2.14]
Chappell 2008	37	158	30	167	5.0%	1.30 [0.85, 2.00]
Russell 2008	126	368	30	139	7.7%	1.59 [1.12, 2.24]
Subtotal (95% CI)		**1109**		**775**	**33.2%**	**1.59 [1.35, 1.88]**
Total events	370		156			
Heterogeneity: Tau² = 0.00; Chi² = 1.33, df = 4 (P = 0.86); I² = 0%						
Test for overall effect: Z = 5.47 (P < 0.00001)						
1.3.2 Milnacipran						
Arnold 2010b	143	516	92	509	17.2%	1.53 [1.22, 1.93]
Branco 2010	112	430	88	446	15.3%	1.32 [1.03, 1.69]
Clauw 2008	224	795	75	401	17.1%	1.51 [1.19, 1.90]
Mease 2009a	241	665	58	223	15.6%	1.39 [1.09, 1.78]
Vitton 2004	27	97	6	28	1.5%	1.30 [0.60, 2.83]
Subtotal (95% CI)		**2503**		**1607**	**66.8%**	**1.44 [1.28, 1.62]**
Total events	747		319			
Heterogeneity: Tau² = 0.00; Chi² = 1.04, df = 4 (P = 0.90); I² = 0%						
Test for overall effect: Z = 6.04 (P < 0.00001)						



Standard Mean Difference in Pain: -.23 (Cohen's: small effect on pain)

Number Needed to Treat: 11 Number Needed to Harm: 11

Population Studies

EJP
European Journal of Pain

ORIGINAL ARTICLE

Longitudinal patterns of analgesic and central acting drug use and associated effectiveness in fibromyalgia

F. Wolfe[1], B.T. Walitt[2], R.S. Katz[3], Y.C. Lee[4], K.D. Michaud[5], W. Häuser[6]

- 3,123 patients with fibromyalgia who participated in a longitudinal study from 2000 to 2011
- 19, 201 semiannual self-report assessments
- All medications measured
- Outcomes: pain, fatigue, physical function
- Analyses:
  - Longitudinal generalized estimating equations (GEE)
  - Sub-analyses of those treated with new central acting drugs (NCAD)

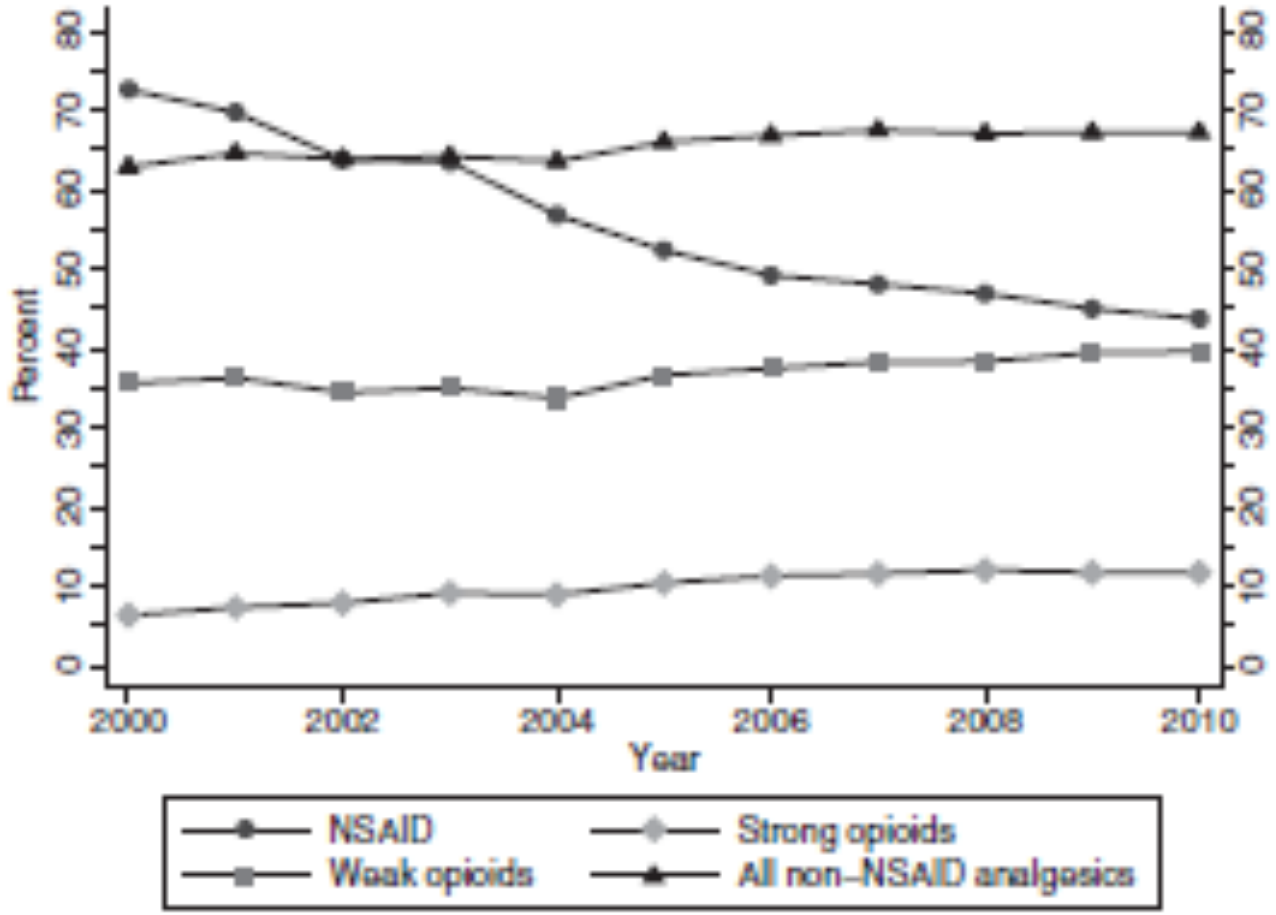


Figure 1 Severity-adjusted percentages of patients using analgesic drugs in 2000–2010. NSAID, nonsteroidal anti-inflammatory drug.

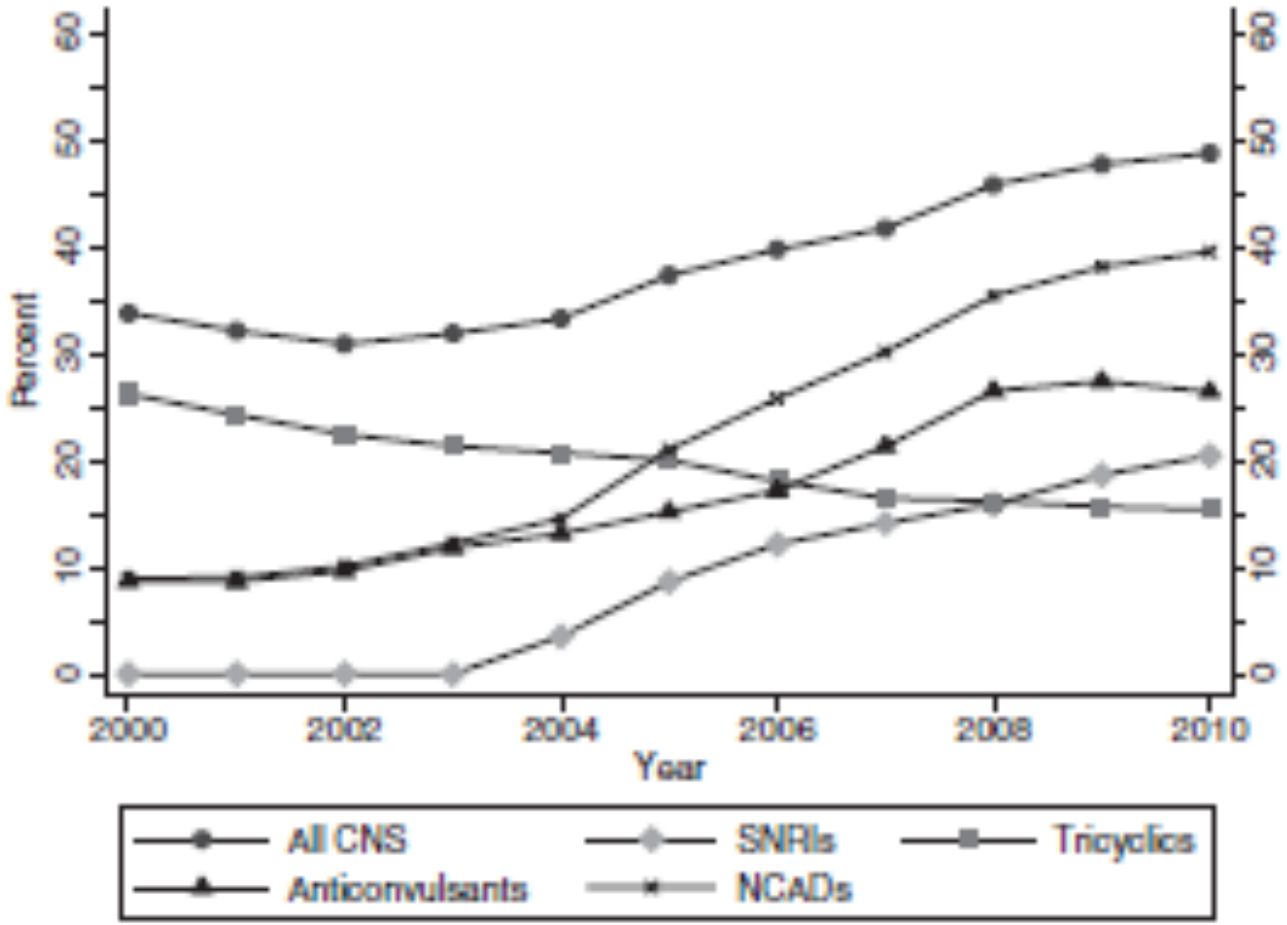


Figure 2 Severity-adjusted percentages of patients using centrally acting drugs in 2000–2010. CNS, central nervous system; NCAD, new central acting drug; SNRI, serotonin–norepinephrine reuptake inhibitor.

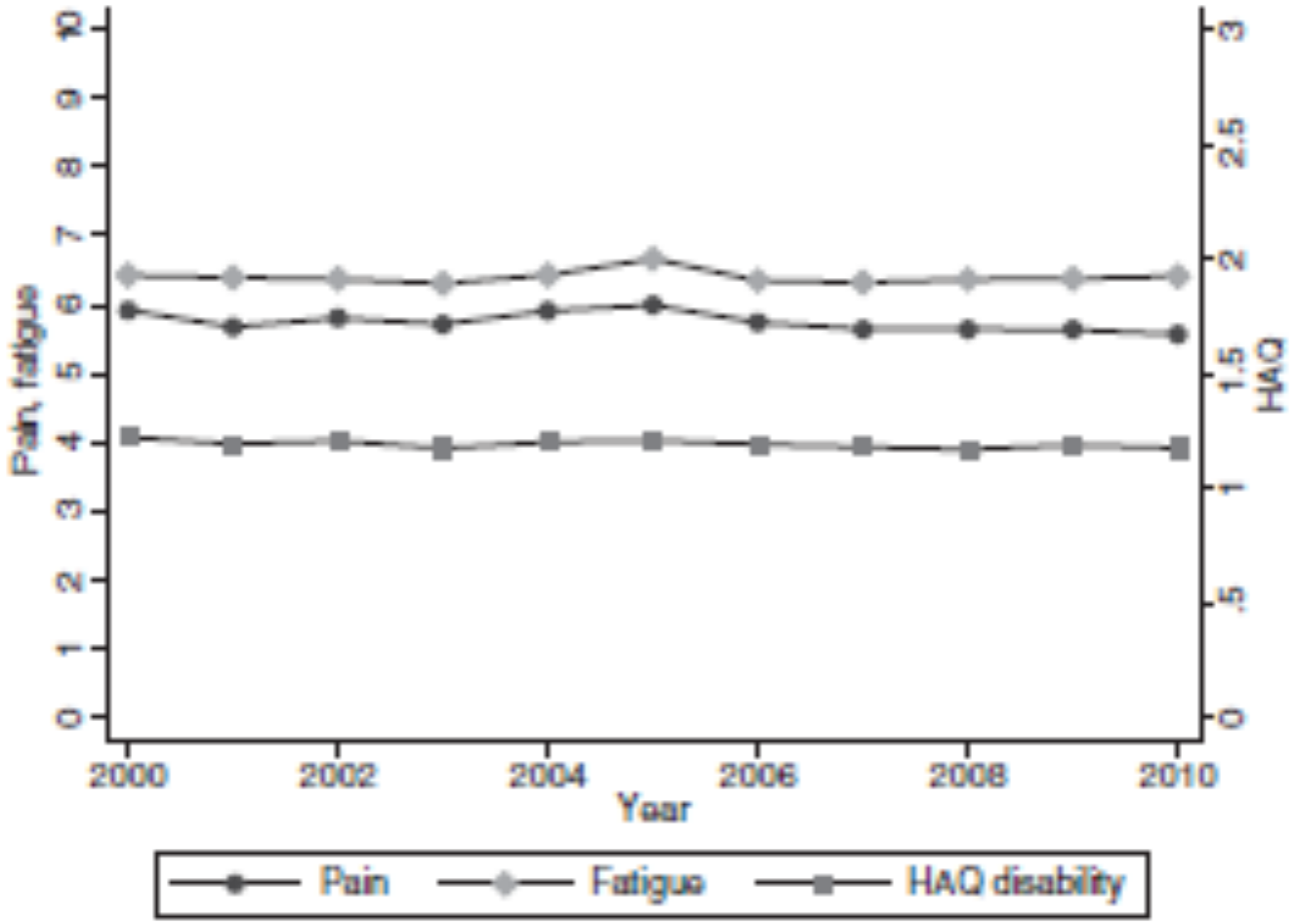


Figure 3 Adjusted mean pain, fatigue and Health Assessment Questionnaire (HAQ) scores of fibromyalgia study patients in 2000–2010.

Table 2 Effect of treatment with NCAD on fibromyalgia outcomes.

Variable	*n*	Group	Pre NCAD[a] Mean (95% CI)	On + Post CAD[a] Mean (95% CI)	Difference (95% CI)	*p*-value
Pain	508	With >0 NCAD	6.21 (6.09, 6.32)	6.04 (5.90, 6.18)	−0.17 (−0.30, −0.03)	0.014
	344	With >1 NCAD	6.22 (6.08, 6.36)	5.99 (5.83, 6.15)	−0.23 (−0.39, −0.08)	0.002
Fatigue	508	With >0 NCAD	6.64 (6.52, 6.76)	6.61 (6.46, 6.76)	−0.03 (−0.17, 0.10)	0.635
	344	With >1 NCAD	6.34 (6.49, 6.78)	6.57 (6.39, 6.74)	−0.07 (−0.22, 0.08)	0.370
HAQ	508	With >0 NCAD	1.28 (1.26, 1.30)	1.30 (1.27, 1.34)	0.02 (−0.01, 0.05)	0.126
	344	With >1 NCAD	1.28 (1.26, 1.31)	1.29 (1.25, 1.33)	0.01 (−0.02, 0.04)	0.609

NCAD: new centrally acting drug – pregabalin, duloxetine, milnacipran. 'With >0 NCAD' refers to patients who used NCAD in at least one 6-month period. 'With >1 NCAD' refers to patients who used NCAD in at least two 6-month periods. CAD, central acting drug; CI, confidence interval; HAQ, Health Assessment Questionnaire.

Means are average adjusted values for study variable before and following the start of CAD therapies.

[a]Pre NCAD = data from observations prior to start of NCAD. On + Post CAD = observations after the start of NCAD whether or not the patient was still using NCAD.

Conclusions

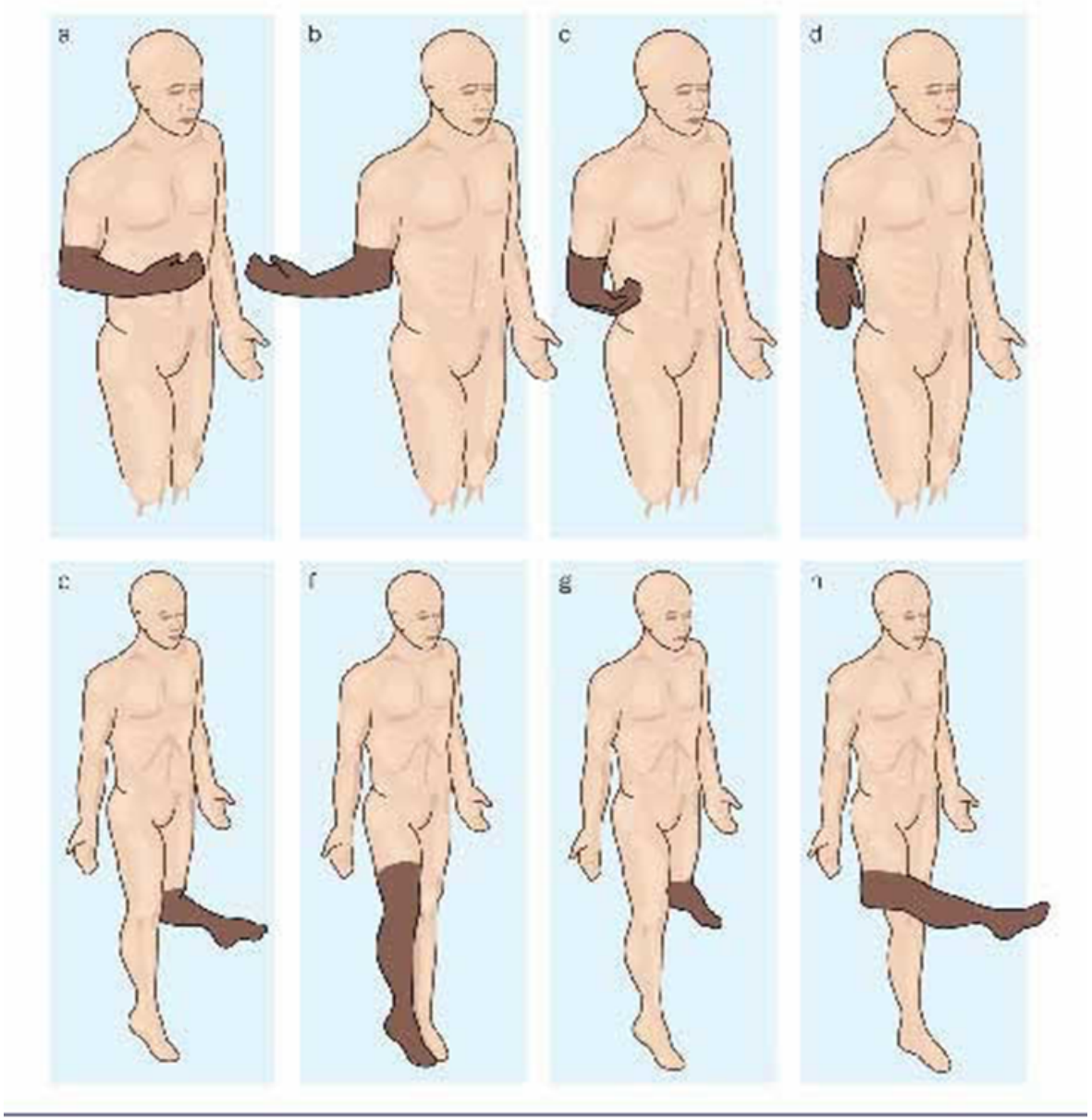
- Functional Pain Disorders encompass a wide array of common disabling syndromes
- Evidence suggests that Functional Pain Disorders share common neurobiological underpinnings
- Unfortunately, treatment targeting these changes has not been particularly effective to date

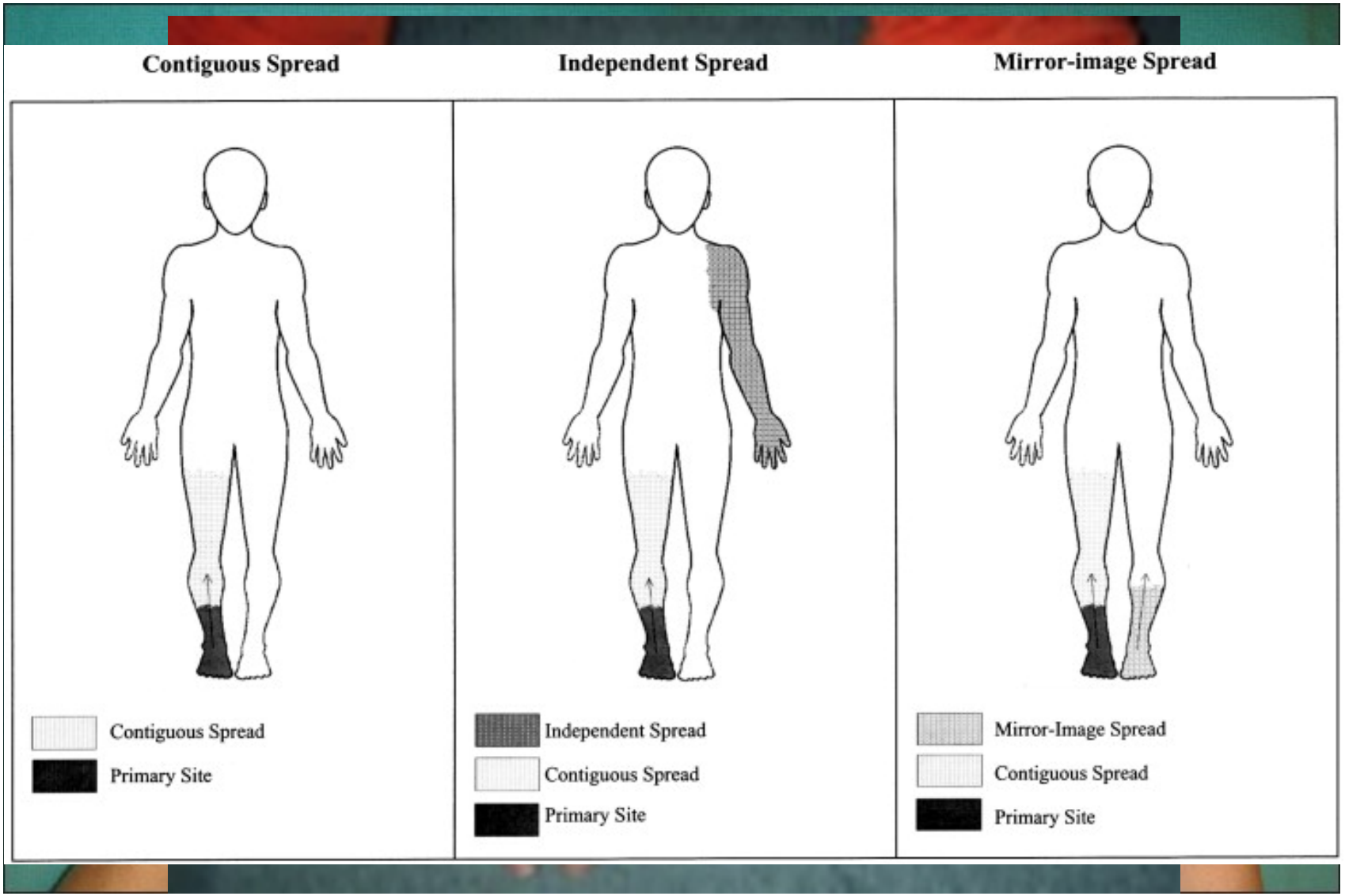
Who ever said stepping on one of these:

is the worst pain ever, has obviously never stepped on one of these:

Extra Slides

Phantom Limb Pain





Complex Regional Pain Syndrome